Expert Second Opinion: ER-Positive and Triple-Negative Breast Cancer

Wednesday, June 23, 2021
5:00 PM – 6:00 PM ET

Faculty

Matthew P Goetz, MD
Hope S Rugo, MD
Melinda Telli, MD

Moderator

Neil Love, MD

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Faculty

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Erivan K Haub Family Professor of Cancer Research
Honoring Richard F Emslander, MD
Professor of Oncology and Pharmacology
Director, Mayo Clinic Breast SPORE
Co-Leader, Women's Cancer Program
Mayo Clinic
Rochester, Minnesota

Melinda Telli, MD
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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Exact Sciences Inc, Lilly, Merck, Novartis, Puma Biotechnology Inc and Seagen Inc.

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Dr Love — Disclosures

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Goetz — Disclosures

No relevant conflicts of interest to disclose.

Dr Rugo — Disclosures

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Honoraria	Mylan, Puma Biotechnology Inc
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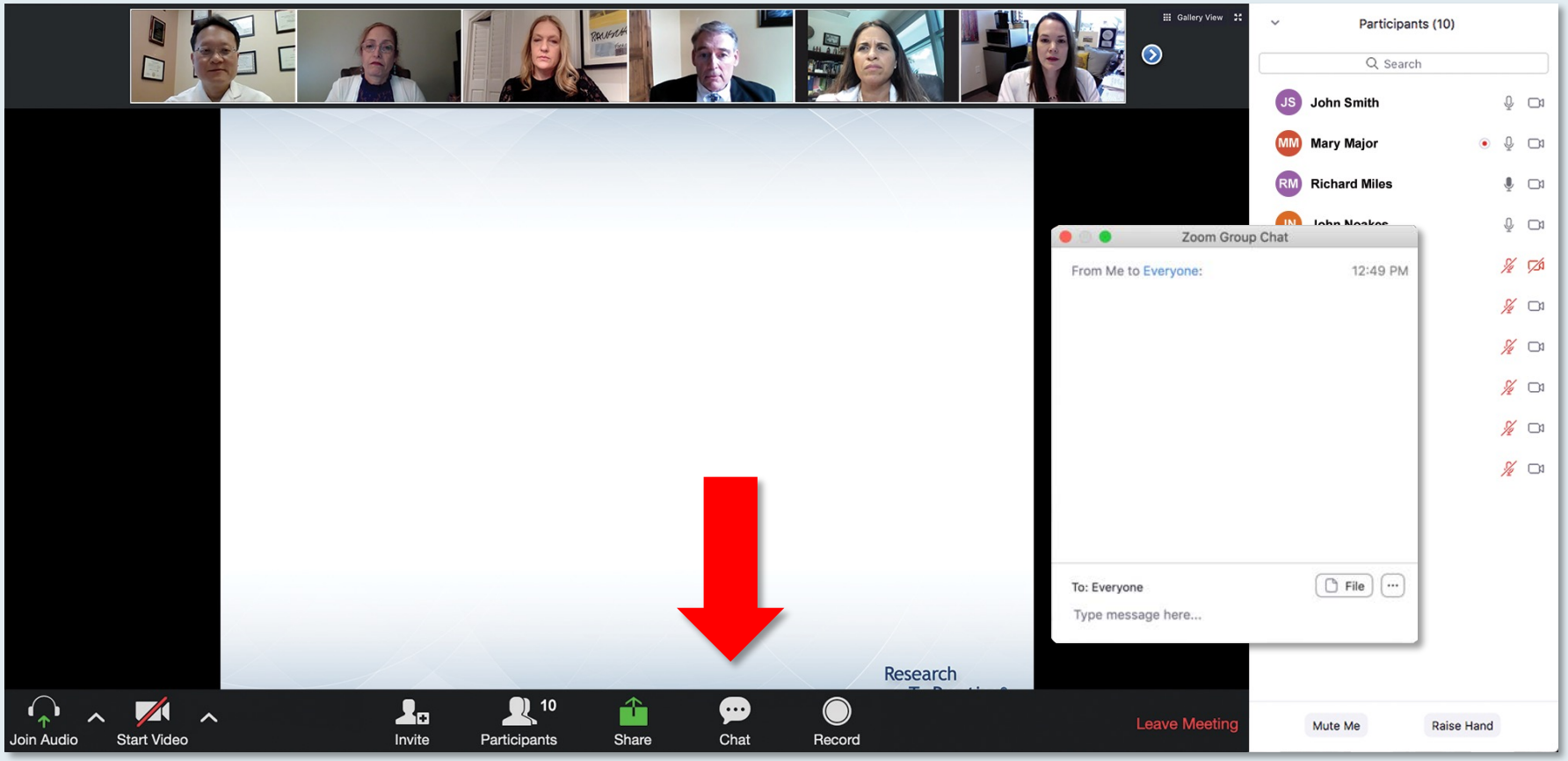
Data and Safety Monitoring Board/Committee	G1 Therapeutics, Immunomedics Inc

We Encourage Clinicians in Practice to Submit Questions



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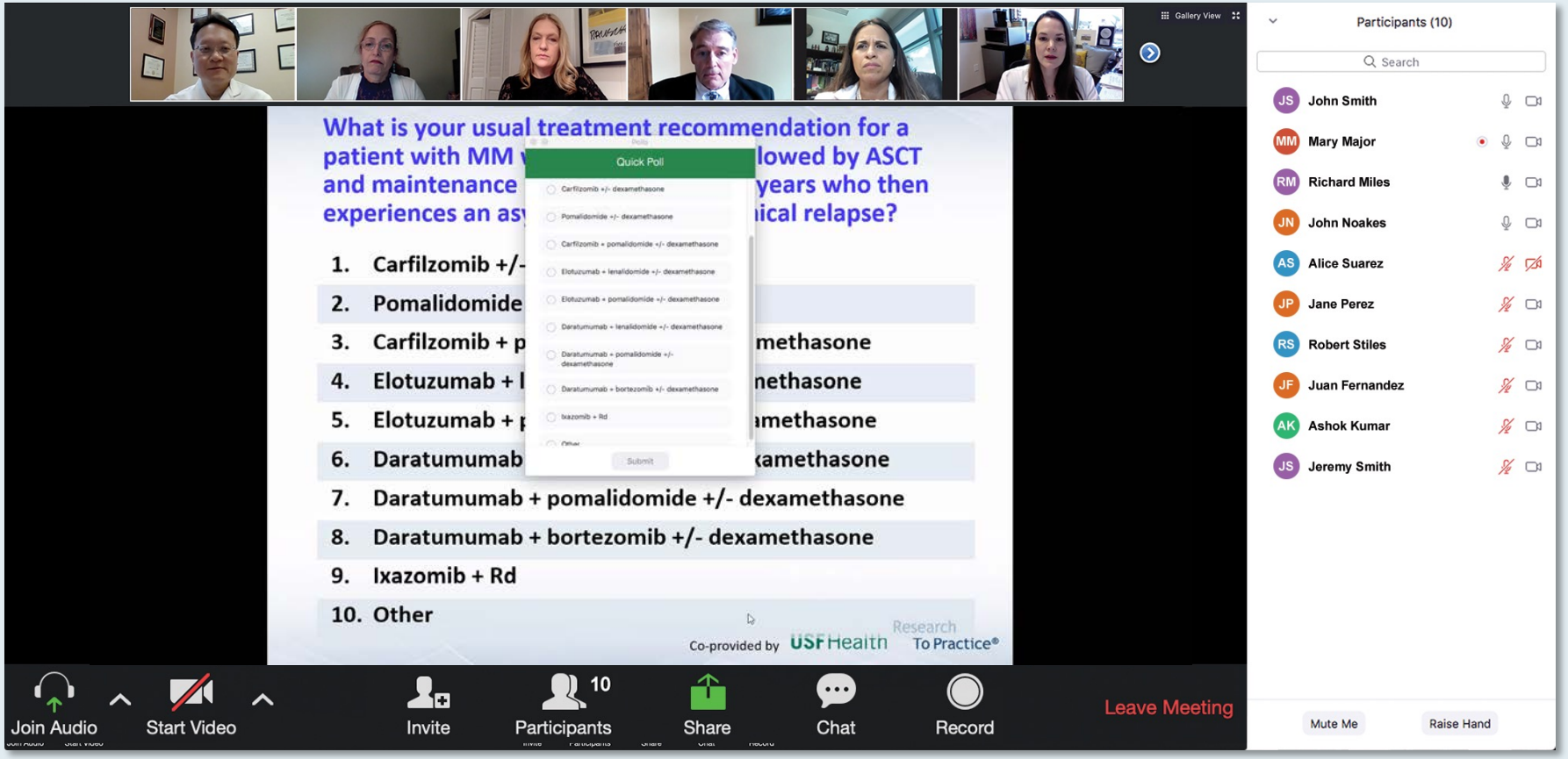

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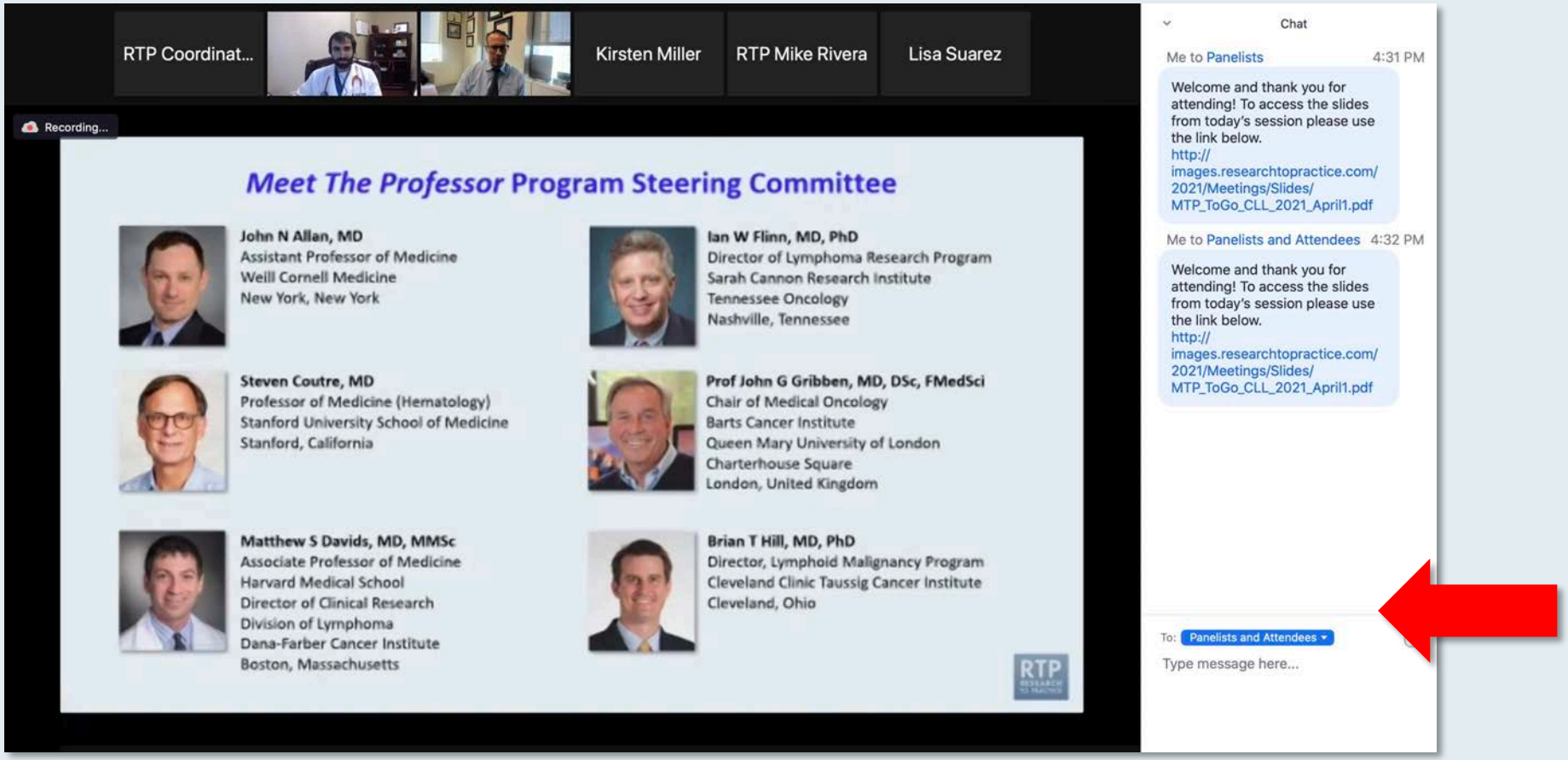

Drag the white line above the submission box up to create more space for your message.

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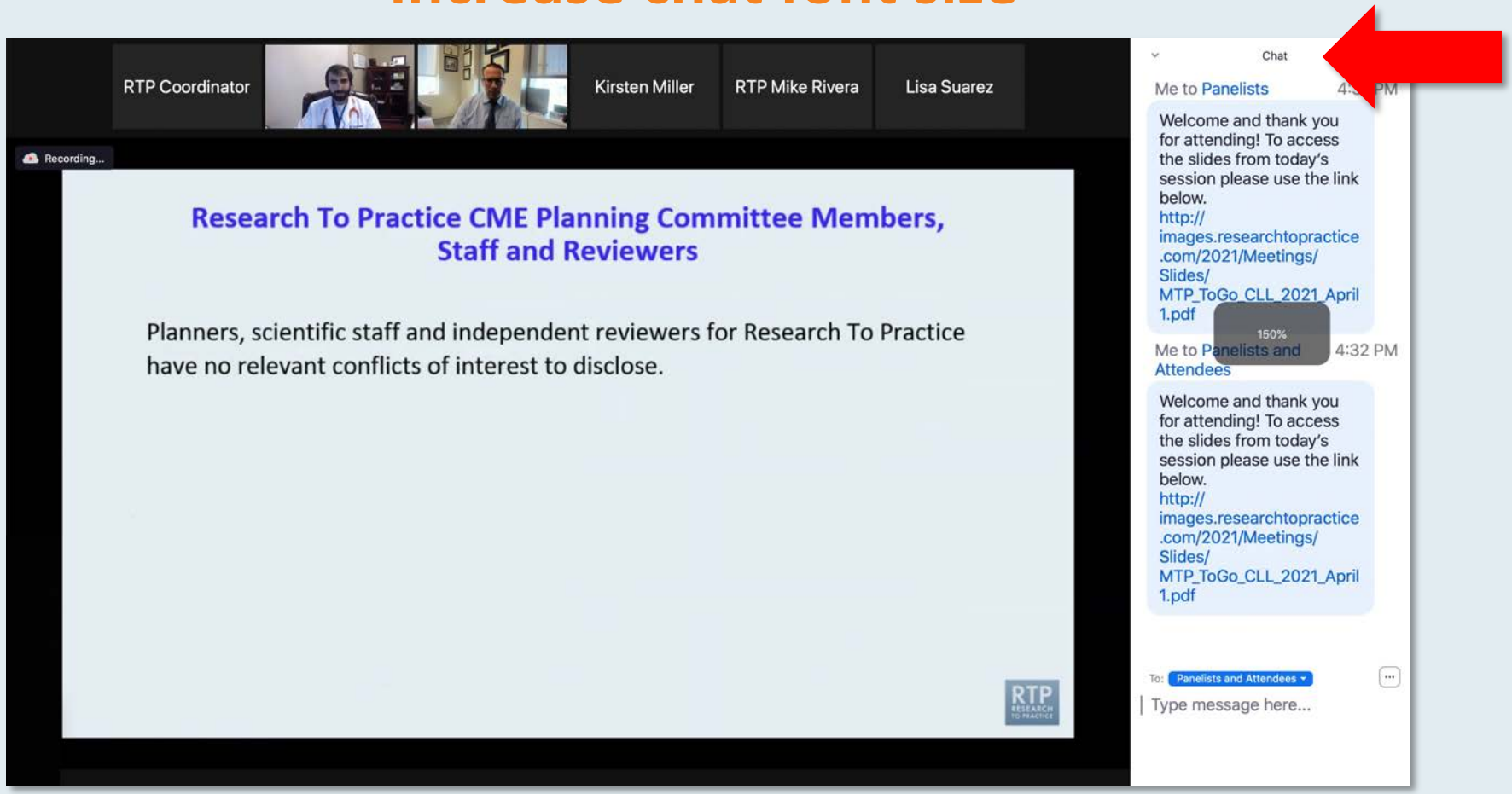
Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

ER-Positive Metastatic Breast Cancer

DR ERIKA HAMILTON

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Multiple Myeloma
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Ovarian Cancer
Wednesday, July 7
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Hormonal Therapy for Prostate Cancer
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Saturday, June 26, 2021
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Video Consensus or Controversy? Chronic Lymphocytic Leukemia and Follicular Lymphoma

Tuesday, June 29, 2021
5:00 PM – 6:00 PM ET

Faculty

Nathan H Fowler, MD
Prof John G Gribben, MD, DSc, FMedSci
Brad S Kahl, MD

Moderator

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Shaji K Kumar, MD
Sagar Lonial, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

In Partnership with Project Echo® and Florida Cancer Specialists

Tuesday, July 6, 2021
5:00 PM – 6:00 PM ET

Faculty

David I Quinn, MBBS, PhD

Moderator

Neil Love, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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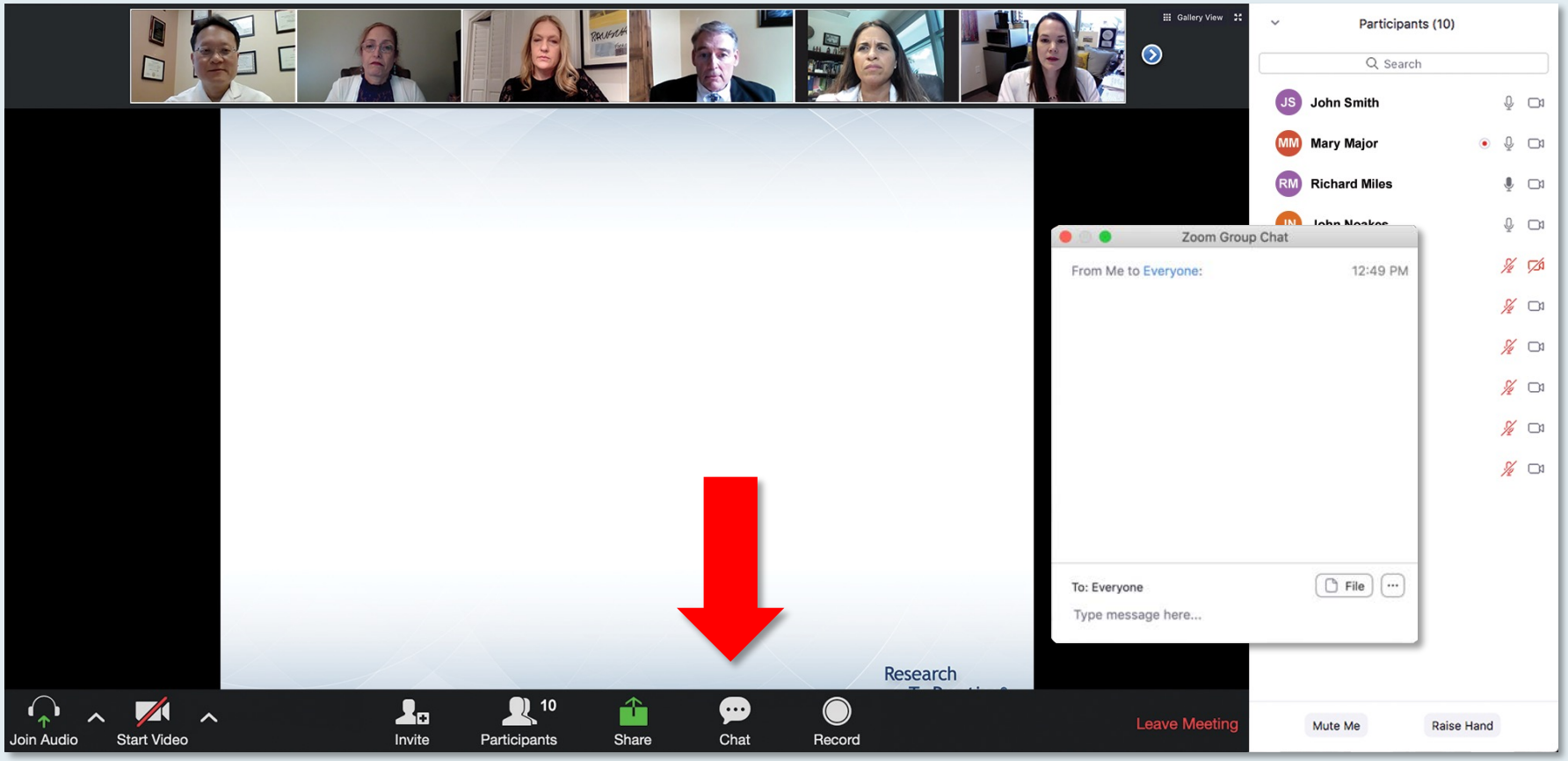

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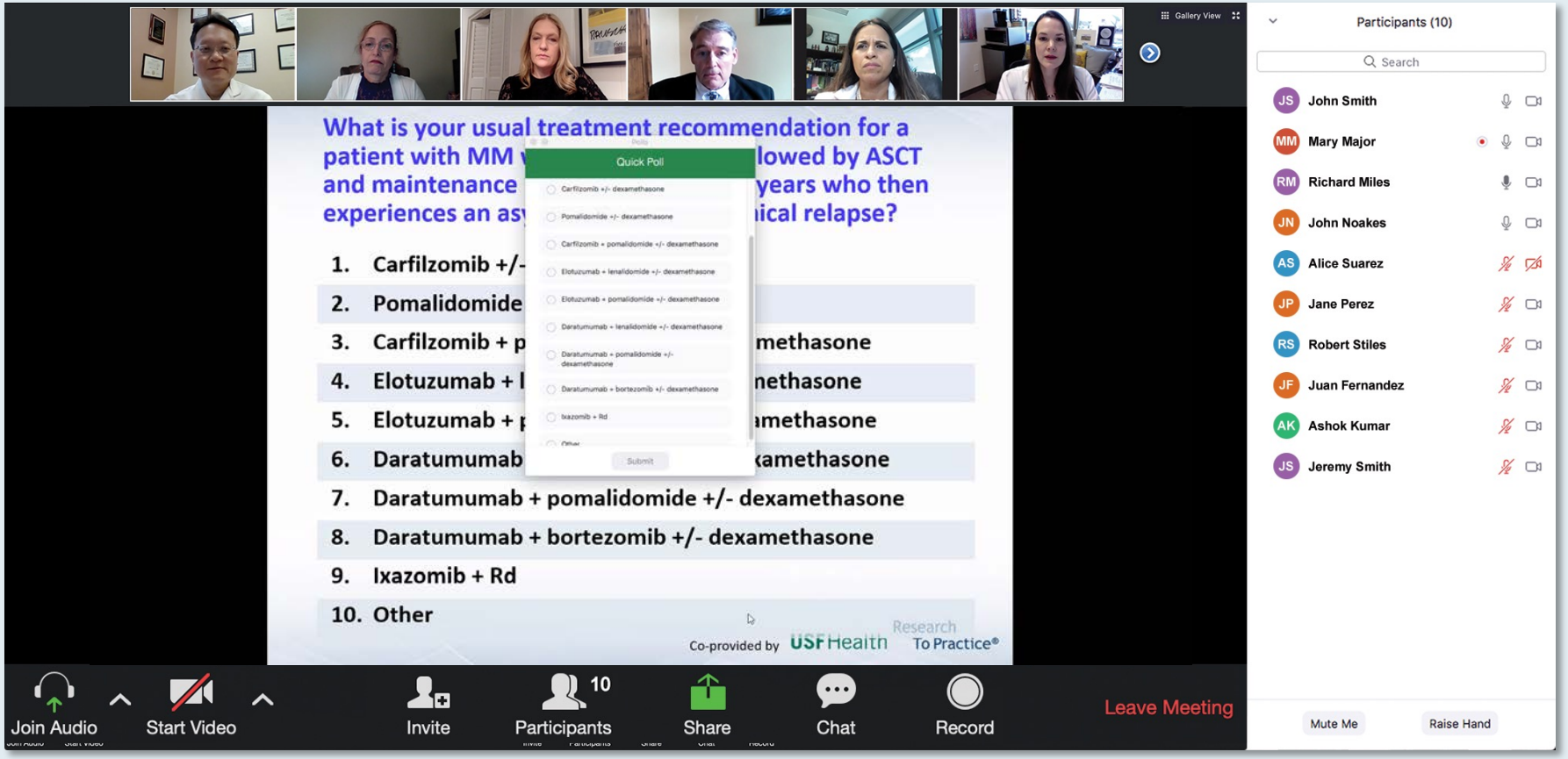

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Michael J Birrer, MD, PhD
Kathleen Moore, MD
Additional faculty to be announced

Moderator

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Contributing Oncologists

Reshma Mahtani, DO
Associate Professor of Medicine
Co-Leader, Breast Cancer Program
Sylvester Cancer Center
University of Miami
Miami, Florida

Ruth O'Regan, MD
Chair, Department of Medicine
Charles A Dewey Professor of Medicine
University of Rochester
Rochester, New York

Ann Partridge, MD, MPH
Vice Chair of Medical Oncology
Director, Program for Young Women with Breast Cancer
Director, Adult Survivorship Program
Dana-Farber Cancer Institute
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Agenda

Module 1: Evolving Clinical Decision-Making for Patients with ER-Positive, HER2-Negative Localized Breast Cancer

- Dr O'Regan: A 54-year-old postmenopausal woman with ER-positive, PR-negative, HER2-negative pT1cN1 breast cancer
- Dr Mahtani: A 43-year-old woman with 6-cm ER-positive, HER2-negative localized breast cancer

Module 2: Selection and Sequence of Therapy for ER-Positive, HER2-Negative Metastatic BC (mBC)

- Dr O'Regan: A 55-year-old woman with ER-positive, PR-negative, HER2-negative mBC
- Dr Mahtani: A 50-year-old woman with ER-positive, HER2-negative mBC – germline BRCA2 mutation
- Dr Partridge: A 37-year-old woman with ER-positive, HER2-negative mBC – germline BRCA1 mutation

Module 3: New Directions in the Treatment of Triple-Negative Breast Cancer (TNBC)

- Dr Partridge: A 52-year-old woman with metastatic TNBC – PD-L1-positive

Considering that it is an indirect comparison, globally how would you compare the efficacy of olaparib for metastatic breast cancer with a germline BRCA mutation to that of osimertinib for metastatic lung cancer with an EGFR mutation?

1. About the same
2. Olaparib is slightly more efficacious
3. Olaparib is much more efficacious
4. Osimertinib is slightly more efficacious
5. Osimertinib is much more efficacious
6. I don’t know

2021 ASCO ANNUAL MEETING

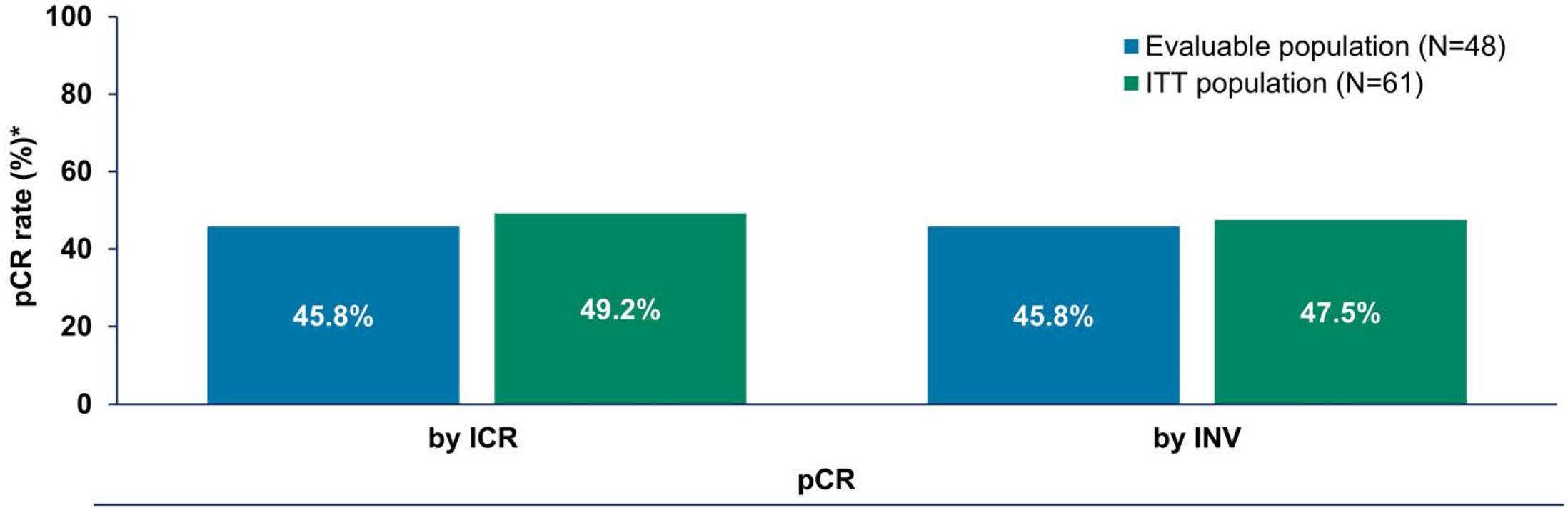
NEOADJUVANT TALAZOPARIB IN PATIENTS WITH GERMLINE *BRCA1/2* MUTATION-POSITIVE, EARLY HER2-NEGATIVE BREAST CANCER: RESULTS OF A PHASE 2 STUDY

Jennifer K. Litton,[1] J. Thaddeus Beck,[2] Jason M. Jones,[3] Jay Andersen,[4] Joanne L. Blum,[5] Lida A. Mina,[6] Raymond Brig,[7] Michael Danso,[8] Yuan Yuan,[9] Antonello Abbattista,[10] Kay Noonan,[11] Jayeta Chakrabarti,[12] Akos Czibere,[13] William F. Symmans,[1] Melinda L. Telli[14]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Highlands Oncology Group, Fayetteville, AR, USA; [3]Avera Cancer Institute, Sioux Falls, SD, USA; [4]Compass Oncology, West Cancer Center, Tigard, OR, USA; [5]Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology Network, Dallas, TX, USA; [6]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [7]Brig Center for Cancer Care and Survivorship, Knoxville, TN, USA; [8]Virginia Oncology Associates, Norfolk, VA, USA; [9]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [10]Pfizer Oncology, Milan, Italy; [11]Pfizer Inc., Groton, CT, USA; [12]Pfizer, Walton Oaks, Surrey, UK; [13]Pfizer Inc., Cambridge, MA, USA; [14]Stanford University School of Medicine, Stanford, CA, USA

June 6, 2021

Pathologic Complete Response



95% CI†	(32.0–60.6)	(36.7–61.6)	(32.0–60.6)	(35.0–60.1)
80% CI†	(36.4–55.2)	(41.0–57.4)		
Posterior probability that true pCR rate exceeds 45%	0.55	0.75		

*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

Courtesy of Melinda Telli, MD

Agenda

Module 1: Evolving Clinical Decision-Making for Patients with ER-Positive, HER2-Negative Localized Breast Cancer

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Module 3: New Directions in the Treatment of Triple-Negative Breast Cancer (TNBC)

- Dr Partridge: A 52-year-old woman with metastatic TNBC – PD-L1-positive

A 52-year-old woman presents with a 2.1-cm Grade II, ER/PR-positive, HER2-negative infiltrating ductal carcinoma (IDC) with 1 positive sentinel lymph node. Would you order a genomic assay for this patient?

1. No, regardless of menopausal status
2. Yes, the 21-gene assay regardless of menopausal status
3. Yes, other genomic assay regardless of menopausal status
4. Yes, the 21-gene assay if postmenopausal
5. Yes, other genomic assay if postmenopausal
6. Yes, other

Which adjuvant therapy would you generally recommend for a postmenopausal woman with a 2.1-cm, Grade II, ER/PR-positive, HER2-negative IDC with 1 positive sentinel node and a 21-gene Recurrence Score® of 10?

1. Tamoxifen
2. Aromatase inhibitor (AI) alone
3. AI + abemaciclib
4. Chemotherapy → endocrine therapy
5. Chemotherapy → AI + abemaciclib
6. Other

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Which adjuvant therapy would you generally recommend for a 54-year-old postmenopausal woman with ER-positive, PR-negative, HER2-negative pT1c breast cancer with 1 positive node and a 21-gene Recurrence Score of 21?

1. Tamoxifen
2. Aromatase inhibitor (AI) alone
3. AI + abemaciclib
4. Chemotherapy → endocrine therapy
5. Chemotherapy → AI + abemaciclib
6. Other

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Case Presentation – Dr O'Regan: A 54-year-old postmenopausal woman with ER-positive, PR-negative, HER2-negative pT1cN1 breast cancer

Dr Ruth O'Regan

- Presents with an abnormal screening mammogram
- Ultrasound confirms 13-mm mass in the right breast
- Biopsy: Grade 2, ER-positive, PR-negative, HER2-negative IDC
- Partial mastectomy with SLNB
  - pT1c, N1 (one node positive)
  - Onco*type* DX® RS: 21

Questions

- In a younger patient with an intermediate Recurrence Score of 21 and node-positive disease, do you believe she should receive adjuvant chemotherapy, or are you comfortable with endocrine therapy alone?
- Would you order any other genomic tests for this patient?

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A 43-year-old woman with 6-cm ER-positive, HER2-negative localized breast cancer receives neoadjuvant AC followed by paclitaxel and at surgery is found to have multifocal residual disease and 1 positive lymph node. In addition to radiation therapy and endocrine treatment, which of the following, if any, would you include as postoperative therapy?

1. Chemotherapy
2. Abemaciclib
3. Both chemotherapy and abemaciclib
4. Neither chemotherapy nor abemaciclib
5. Other

Case Presentation – Dr Mahtani: A 43-year-old woman with 6-cm ER-positive, HER2-negative localized breast cancer

Dr Reshma Mahtani

- Presented with palpable right breast mass, and by MMG/US the lesion was 6 cm with associated pleomorphic calcifications, right axillary node abnormal
  - Biopsy of mass and axillary node: IDC, grade 3, ER+/PR+/HER2 negative
  - No distant disease on staging scans
- Neoadjuvant AC followed by paclitaxel → bilateral mastectomy with right ALND
  - Multi-focal residual disease noted, 1-2 mm with multiple areas of residual DCIS, 1/25 nodes with ITCs

Questions

- How are you using the data from monarchE and KATHERINE for the management of patients with a very good response to neoadjuvant therapy?
- Are you using genomic assays to aid in treatment decisions in the neoadjuvant setting?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

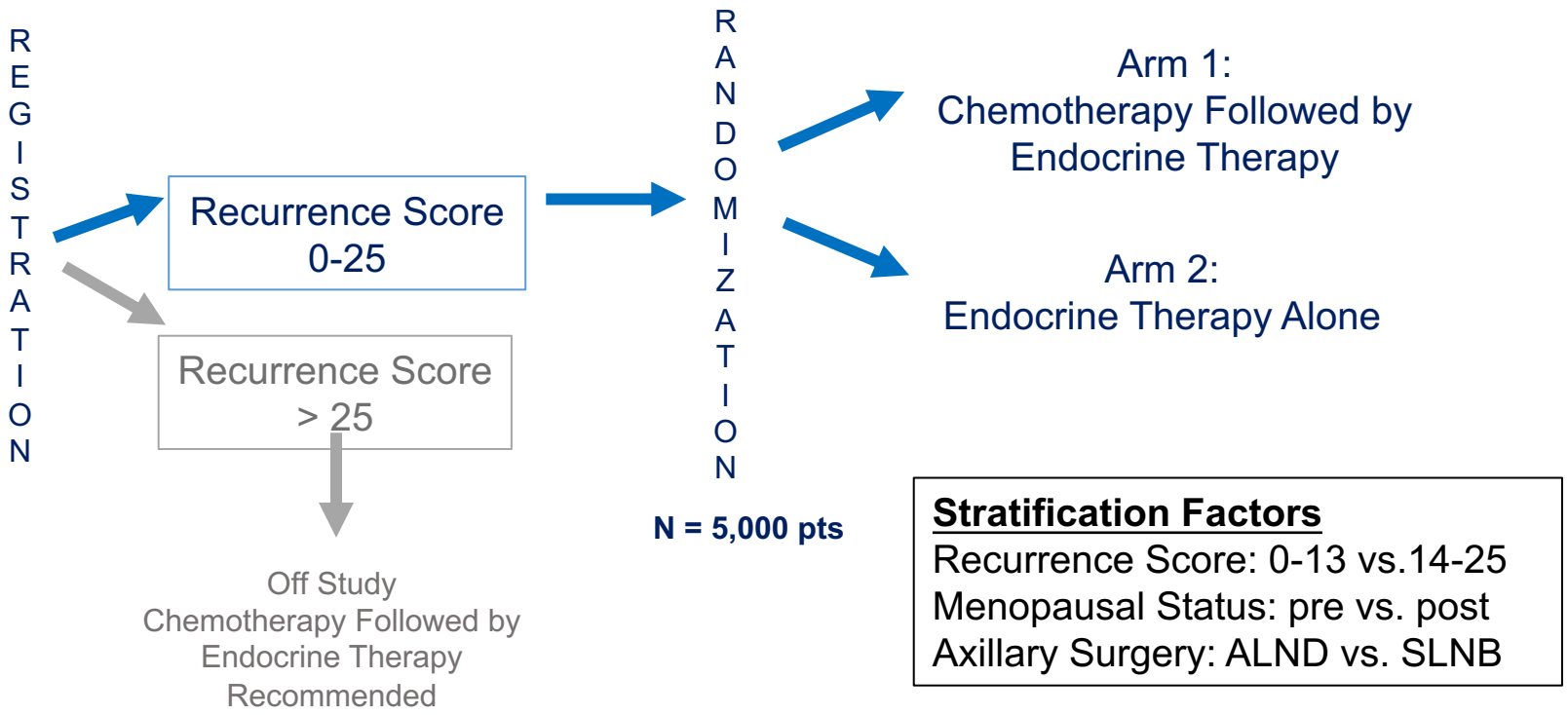
J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

N Engl J Med 2018;379:111-21.

RxPONDER Schema

Key Entry Criteria

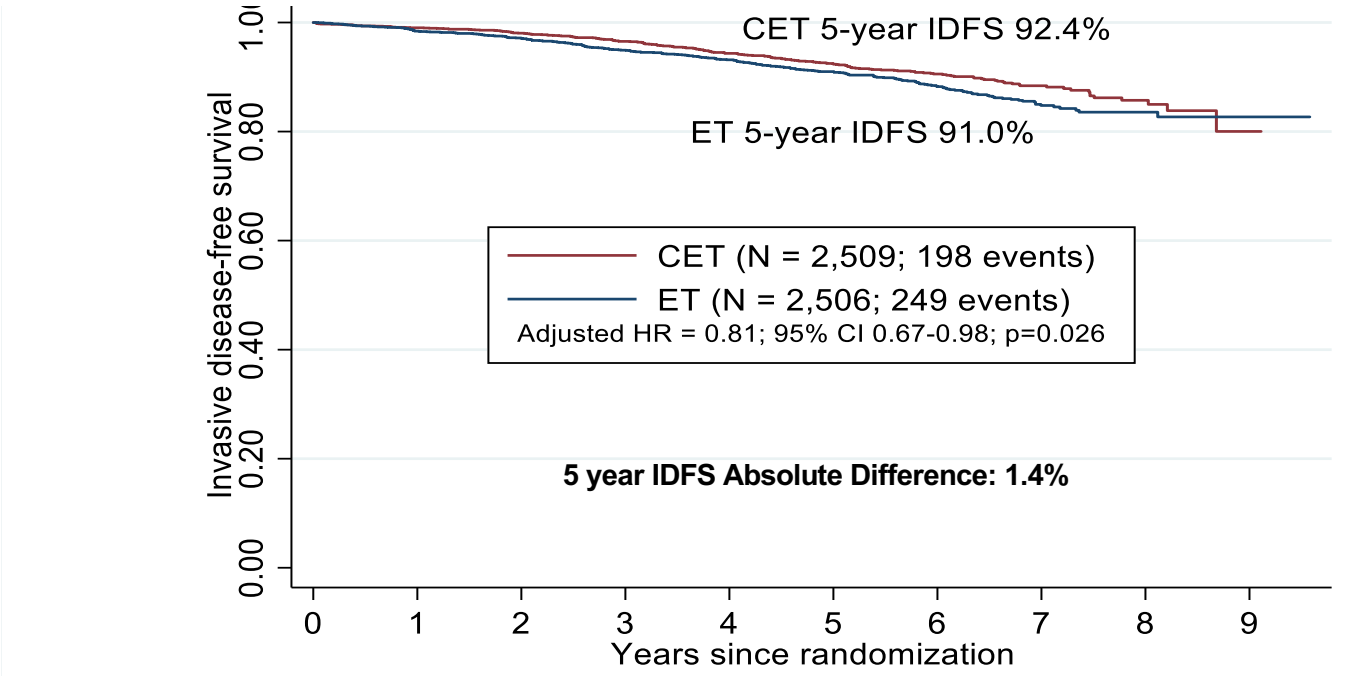
- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND



Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

RxPONDER: IDFS in Overall Population by Treatment Arm

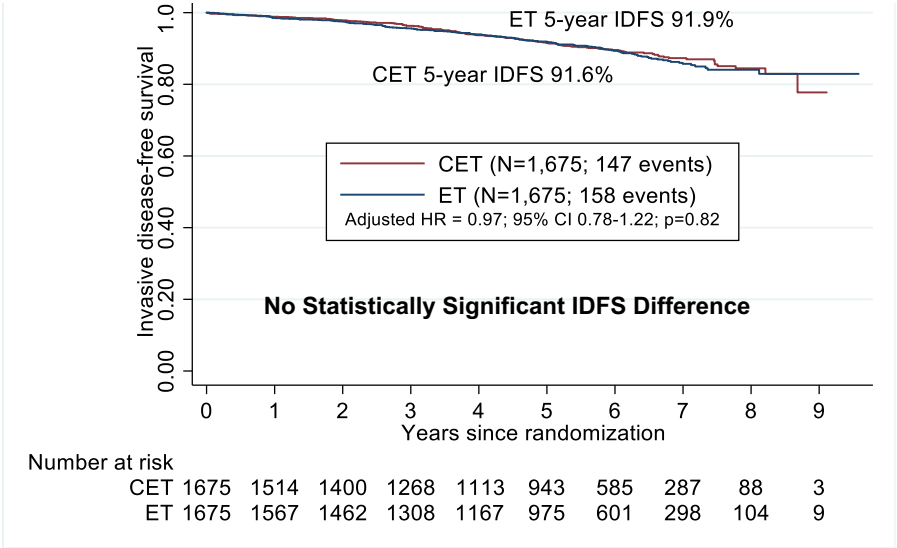


CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

RxPONDER: IDFS Stratified by Menopausal Status

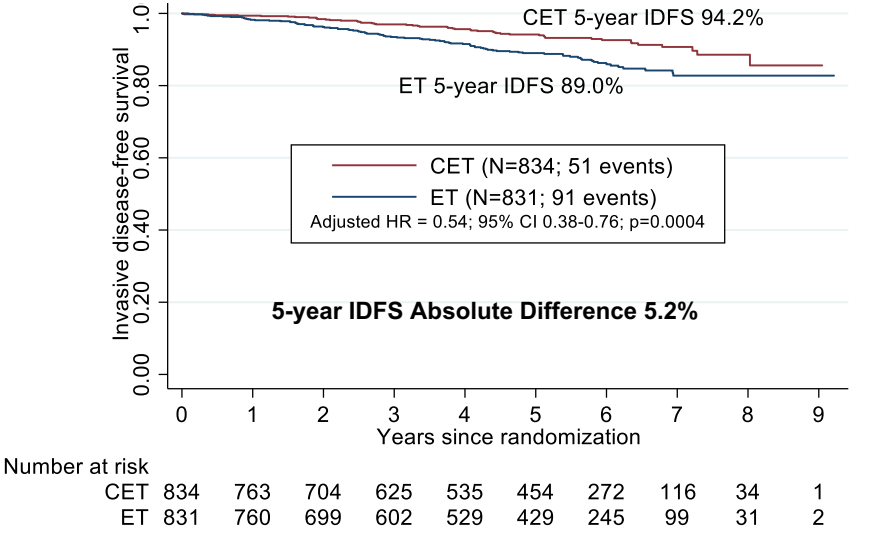
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal

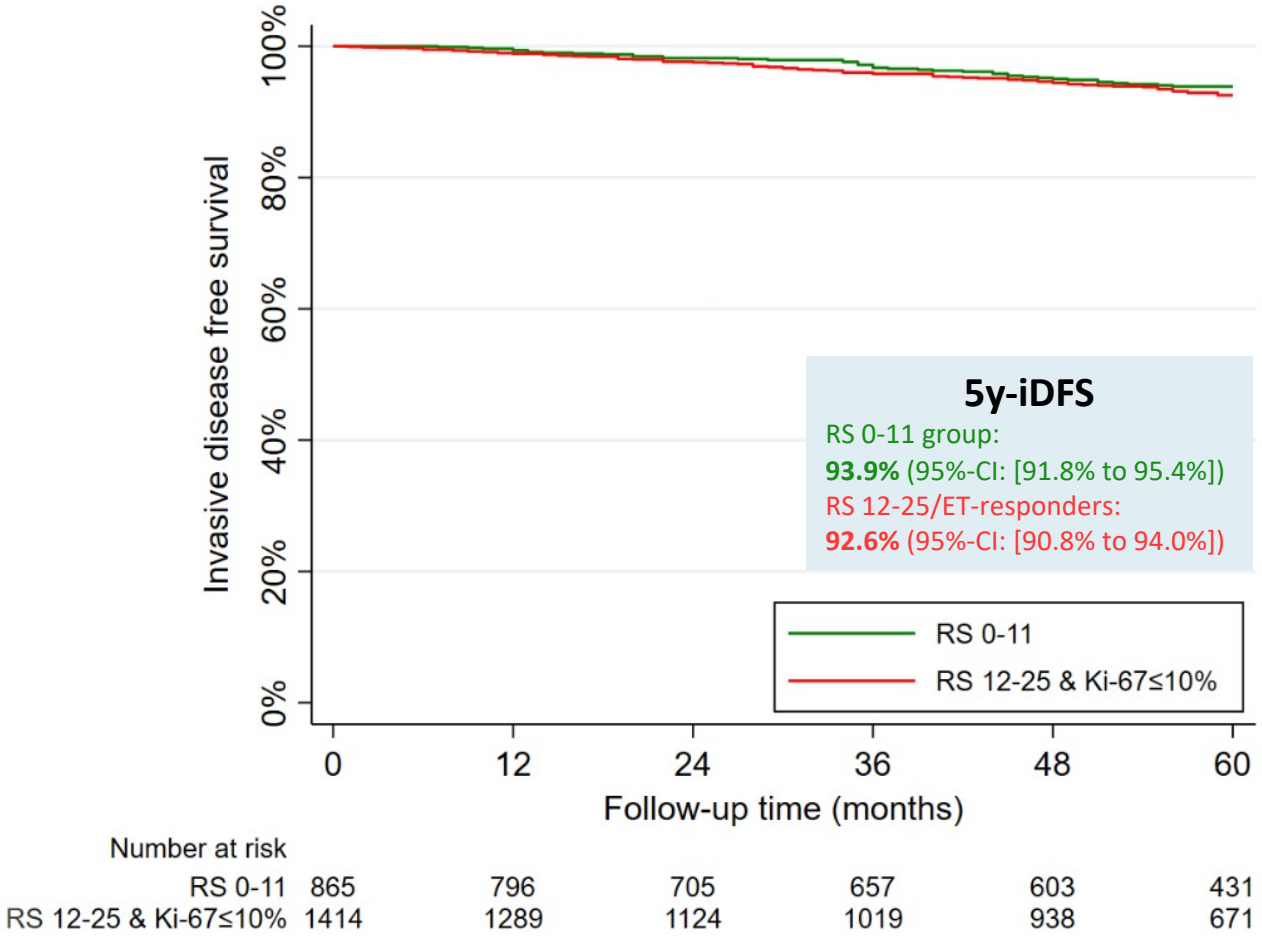


IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

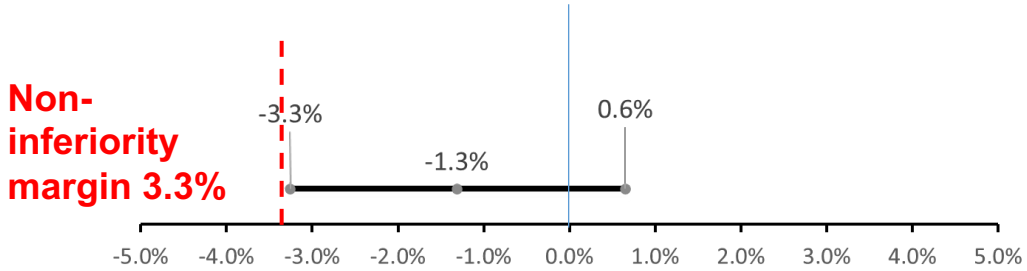
ADAPT HR+/HER2-

Primary endpoint: 5-year iDFS



5y-iDFS

RS 0-11 group:
93.9% (95%-CI: [91.8% to 95.4%])
RS 12-25/ET-responders:
92.6% (95%-CI: [90.8% to 94.0%])



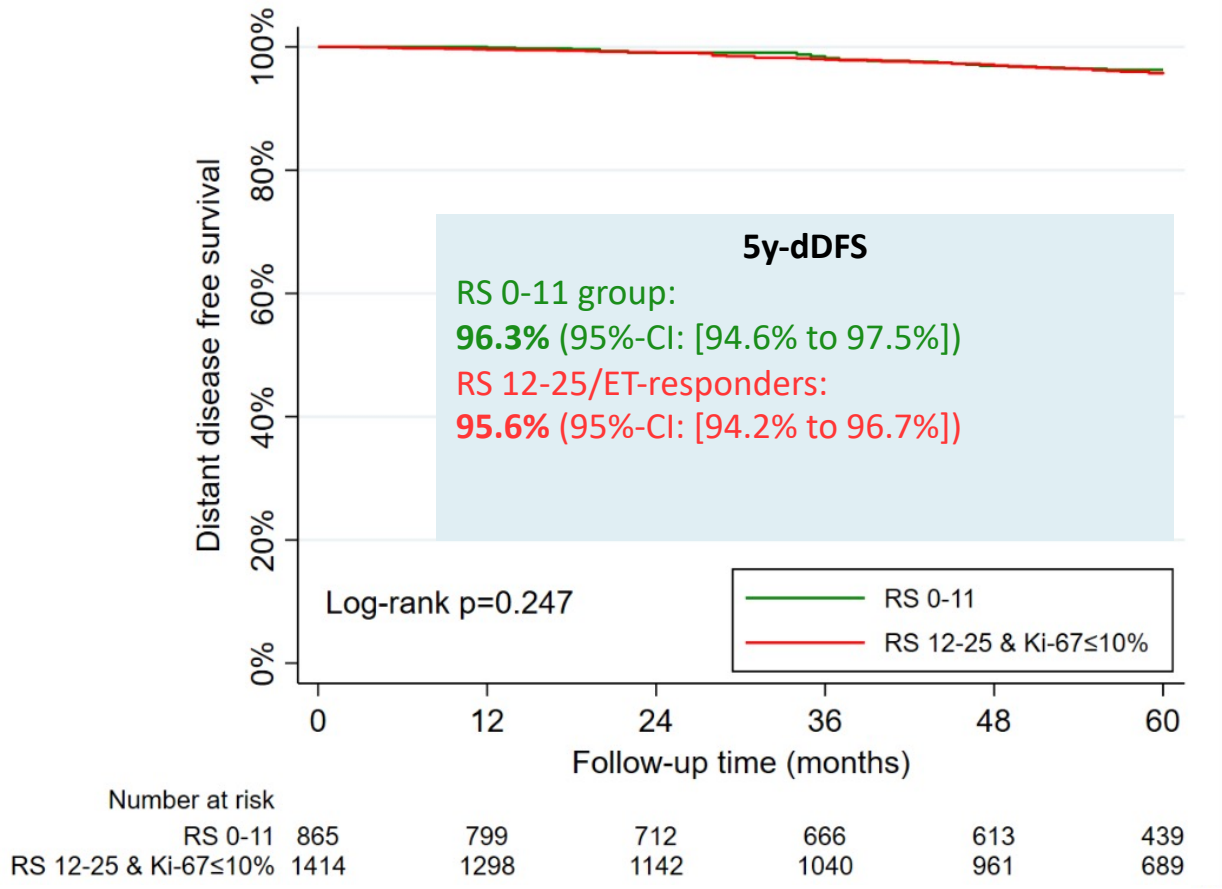
Trial Hypothesis: 5y-iDFS Noninferiority

95%-LCL of 5y-iDFS difference: -3.3%
(RS12-25/ET-responders vs. RS0-11)

The one-sided lower 95% confidence limit of the observed 5y-iDFS difference (-1.3%) was -3.3%; thus, the pre-specified criterion to accept the primary NI-hypothesis was met (p=.05).

ADAPT HR+/HER2-
Distant disease-free and overall survival

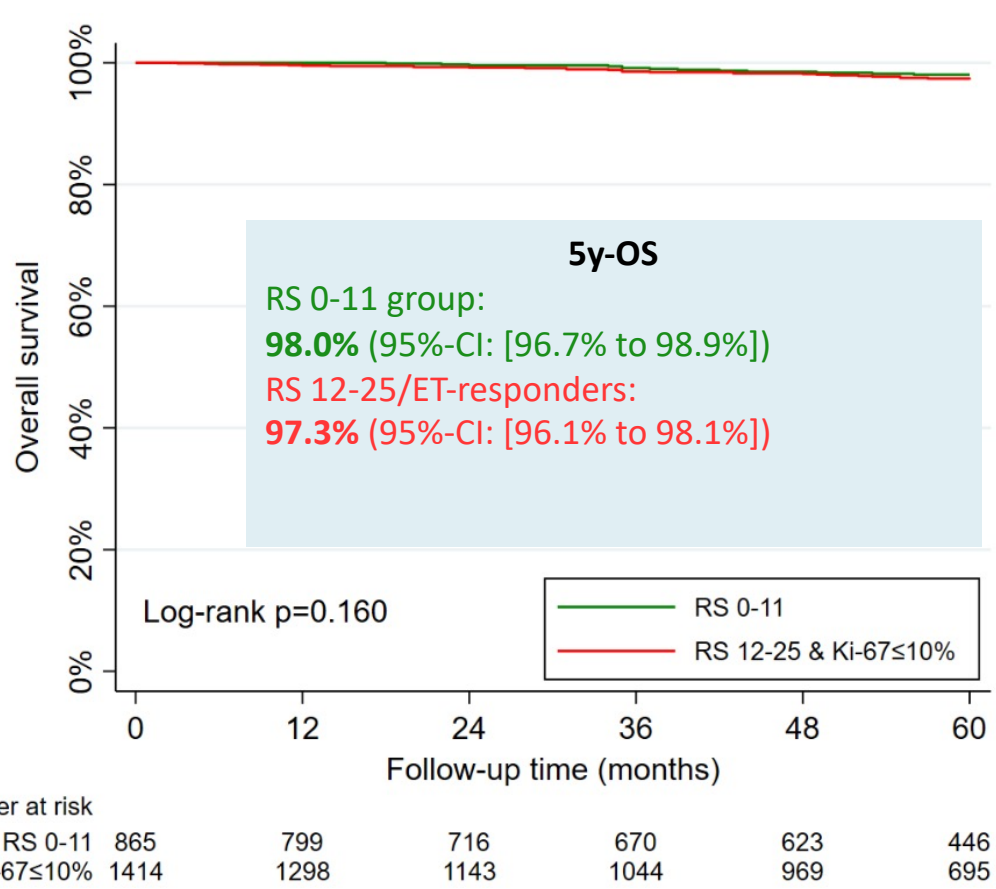
dDFS



Number at risk

RS 0-11	865	799	712	666	613	439
RS 12-25 & Ki-67≤10%	1414	1298	1142	1040	961	689

OS



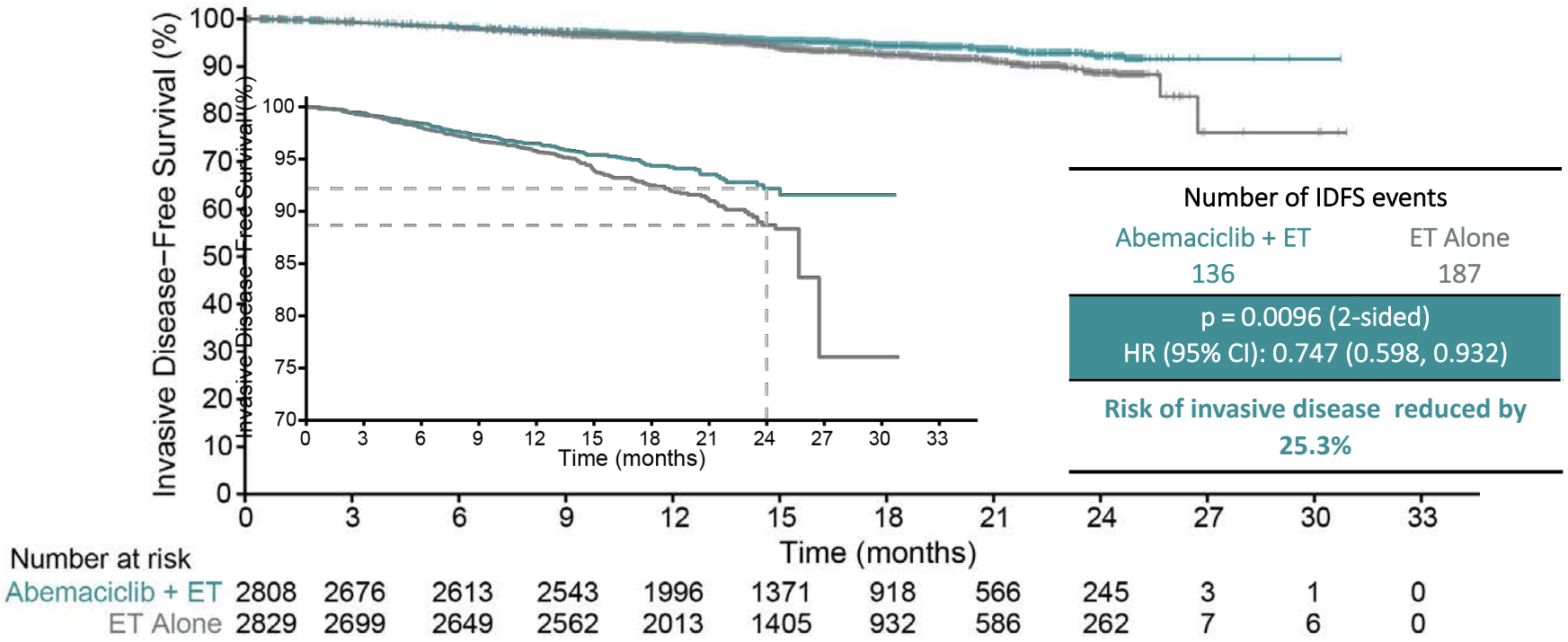
Number at risk

RS 0-11	865	799	716	670	623	446
12-25 & Ki-67≤10%	1414	1298	1143	1044	969	695

MonarchE: Invasive Disease-Free Survival

Median follow up at the interim analysis: ~15.5 months in each arm

- **12.5% of patients had completed the 2-year treatment period**
- **Over 70% of patients were still in 2-year treatment period**



Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference

Courtesy of Matthew P Goetz, MD

Johnston et al. J Clin Oncol 2020

MonarchE: Patients who received neoadjuvant chemotherapy (NAC)

Abemaciclib combined with
adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC)

Miguel Martin[1], Roberto Hegg[2], Sung-Bae Kim[3], Michael Schenker[4], Daniela Grecea[5], Jose Angel Garcia-Saenz[6], Konstantinos Papazisis[7], QuChang Ouyang[8],
Aleksandra Lacko[9], Berna Oksuzoglu[10], James Reeves[11], Meena Okera[12], Laura Testa[13], Chikako Shimizu[14], Ran Wei[15], Tammy Forrester[15], Maria Munoz[15],
Annamaria Zimmermann[15], Desiree Headley[15], Stephen Johnston[16]

Martin M et al. ASCO 2021;Abstract 517.

MonarchE: Patient Population and Analyses

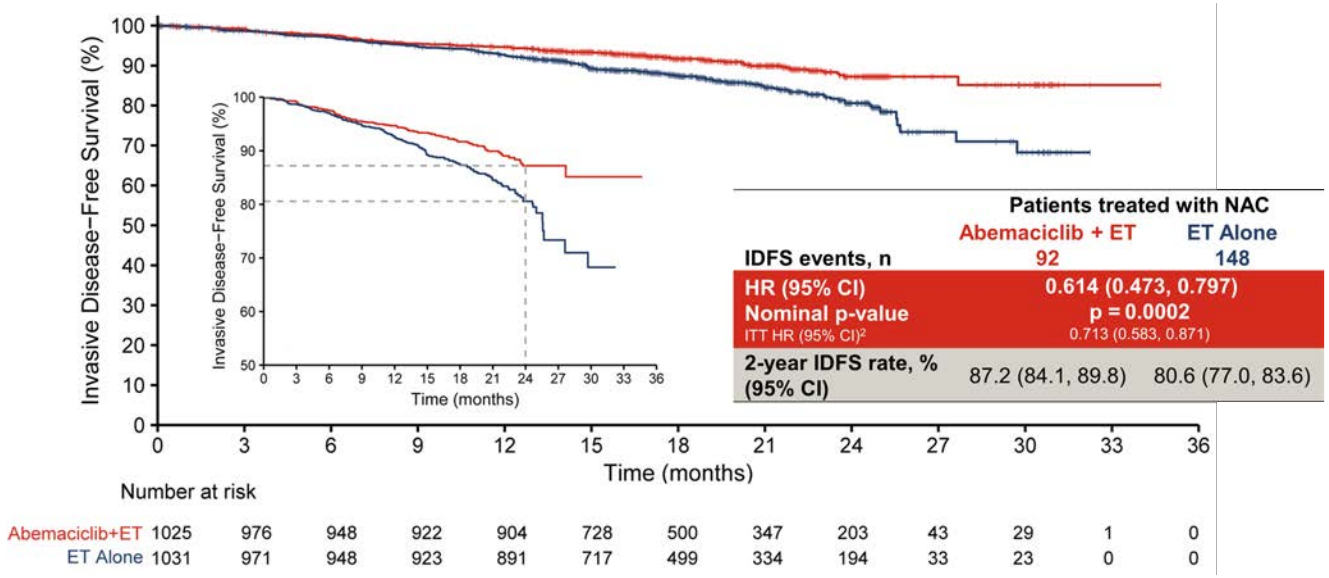
- monarchE patient population:
  - Patients with ≥4 positive axillary lymph nodes (ALN), or 1-3 ALN and either tumor size ≥5 cm, Grade 3 disease, or central Ki-67 ≥20%
  - Prior chemotherapy (NAC, adjuvant, none) was one of the stratification factors
  - 2056 patients received NAC (36% of the monarchE ITT population)

- Within the patients who received NAC, the treatment effect of abemaciclib plus ET was evaluated using Cox Proportional Hazard model and Kaplan-Meier method, in terms of IDFS and DRFS

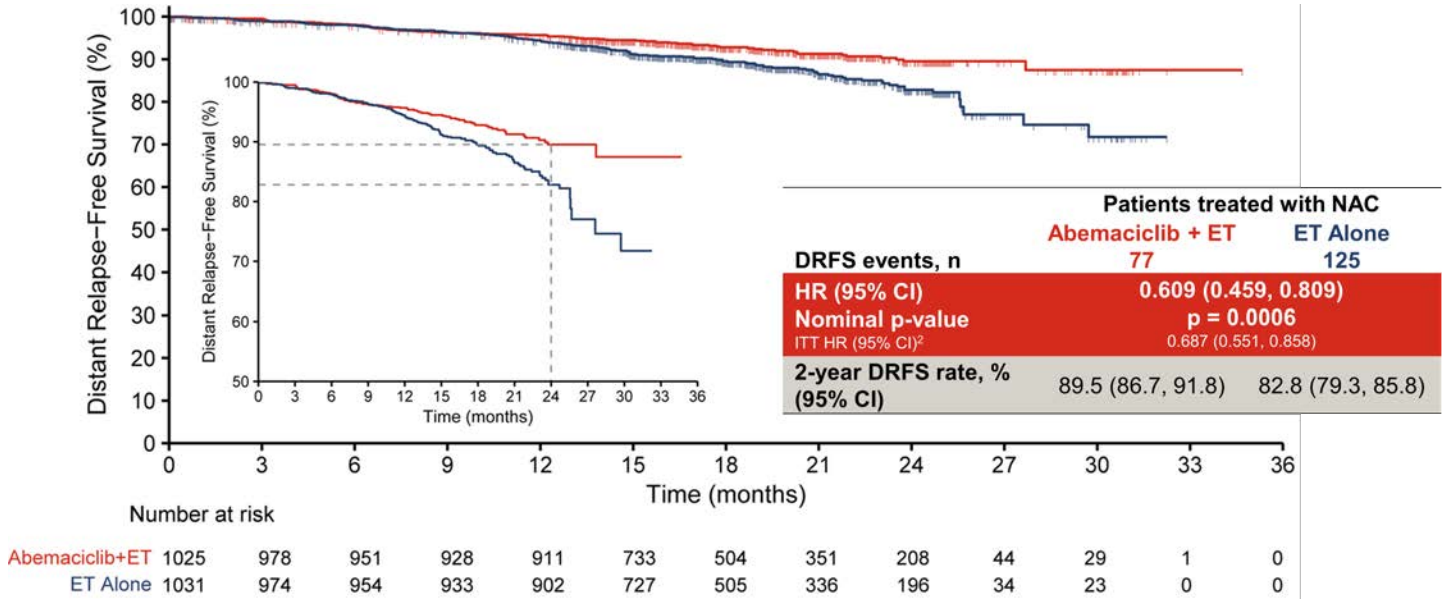
Prior NAC received, n (%)	Abemaciclib + ET N=1025	ET Alone N=1031
Anthracycline + Taxane	903 (88.1)	931 (90.3)
Anthracycline (without Taxane)	71 (6.9)	59 (5.7)
Taxane + Cyclophosphamide	28 (2.7)	23 (2.2)
Other[a]	23 (2.2)	18 (1.7)

Courtesy of Matthew P Goetz, MD

MonarchE: IDFS/DRFS in Patients Who Received NAC



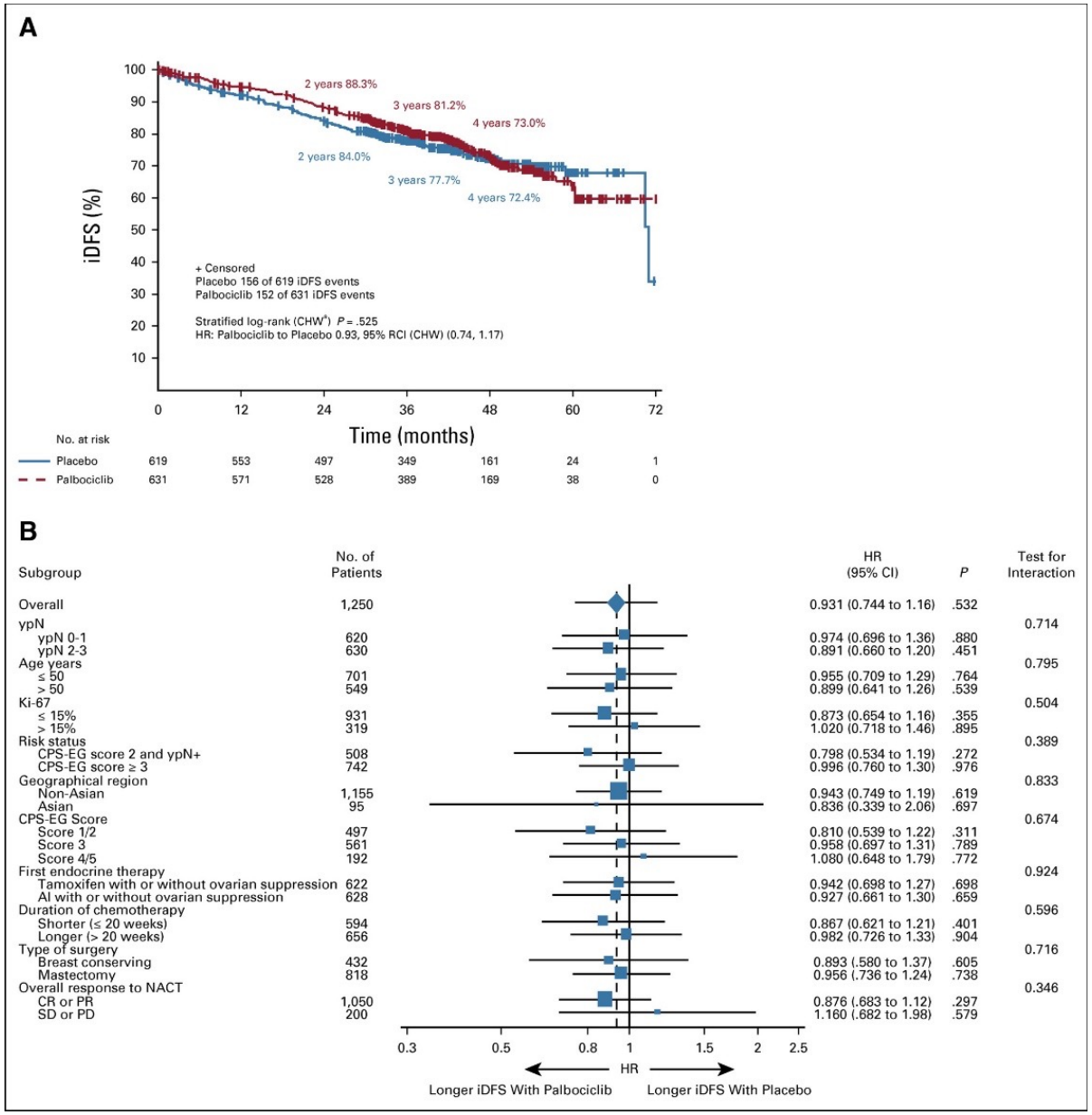
Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference

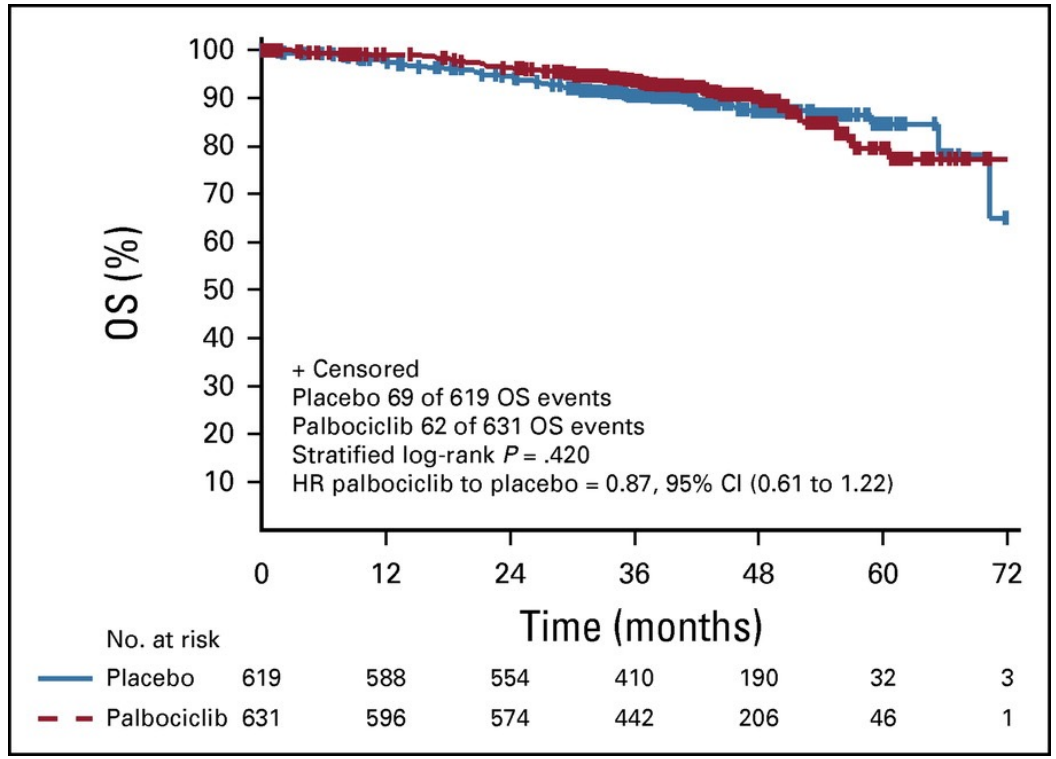


Two-year DRFS rates were 89.5% in the abemaciclib + ET arm and 82.8% in ET arm – 6.7% difference

Courtesy of Matthew P Goetz, MD

PENELOPE-B: IDFS and OS





Loibl J Clin Oncol 2021

Courtesy of Matthew P Goetz, MD

Regulatory and reimbursement issues aside, to which of the following patients with breast cancer and a BRCA germline mutation would you offer adjuvant olaparib?

1. A patient with TNBC and residual disease after neoadjuvant therapy
2. A patient with ER-positive, HER2-negative, node-negative breast cancer and a high Recurrence Score
3. Both
4. Neither

Regulatory and reimbursement issues aside, to which of the following patients with ER-positive, HER2-negative breast cancer and 2 positive nodes would you offer adjuvant olaparib?

1. A patient with a somatic BRCA mutation
2. A patient with a PALB2 mutation
3. Both
4. Neither

BIG Breast International Group

frontier science

NRG ONCOLOGY Advancing Research. Improving Lives.

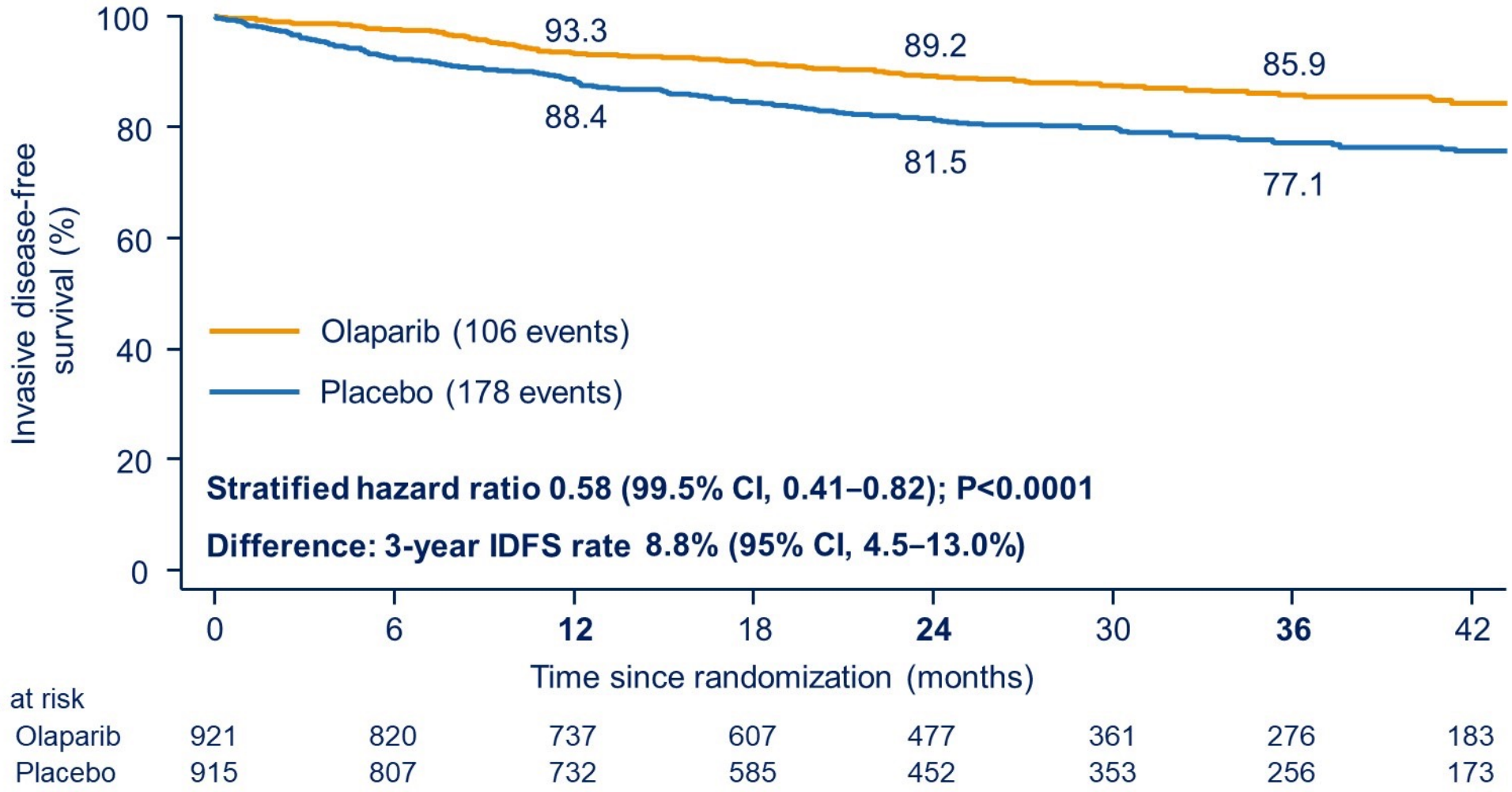
NIH NATIONAL CANCER INSTITUTE

A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

OlympiA: Invasive disease-free survival (ITT)



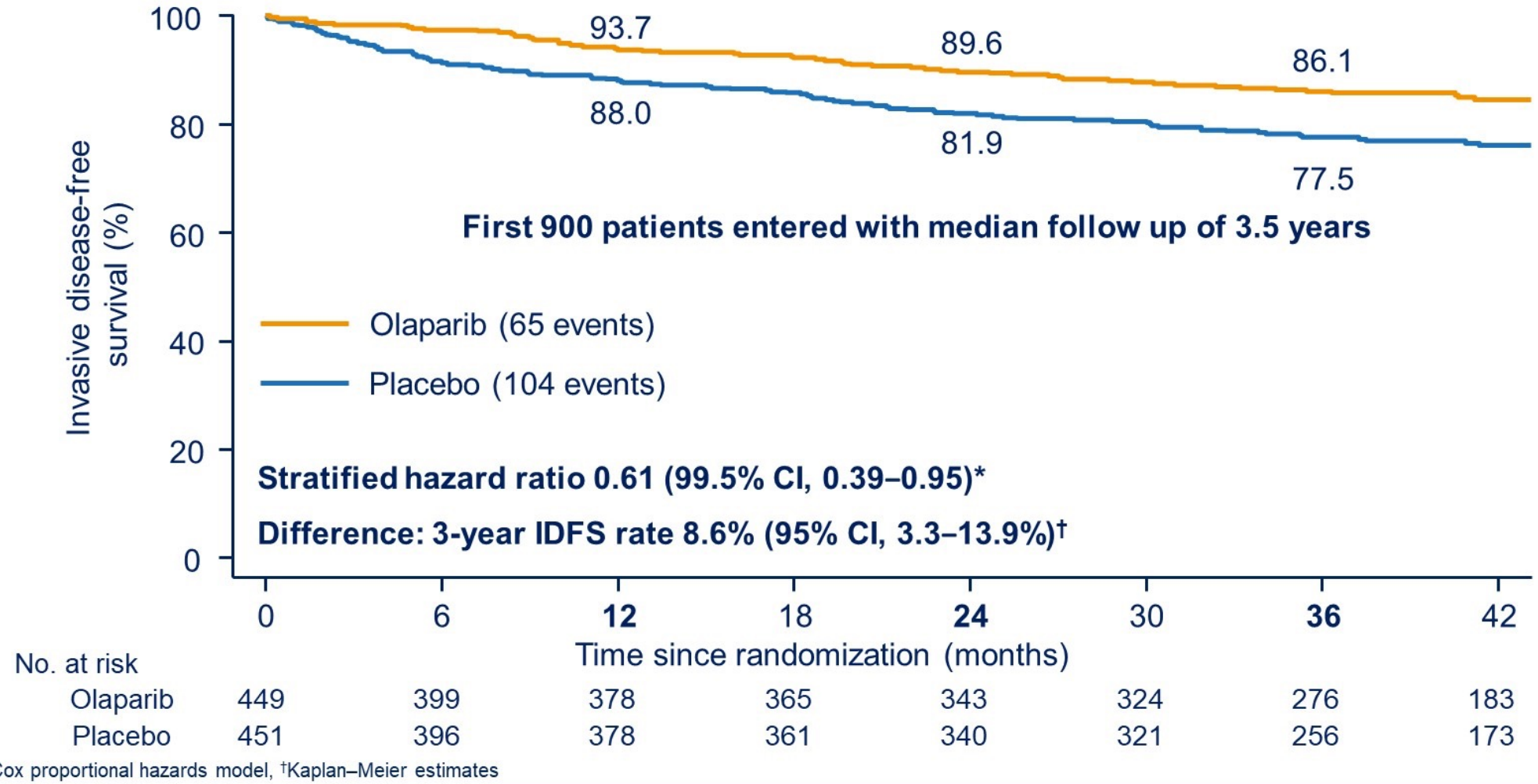
No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

OlympiA: Invasive disease-free survival (mature cohort)



*Stratified Cox proportional hazards model, †Kaplan–Meier estimates

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

OlympiA: Distant disease-free survival

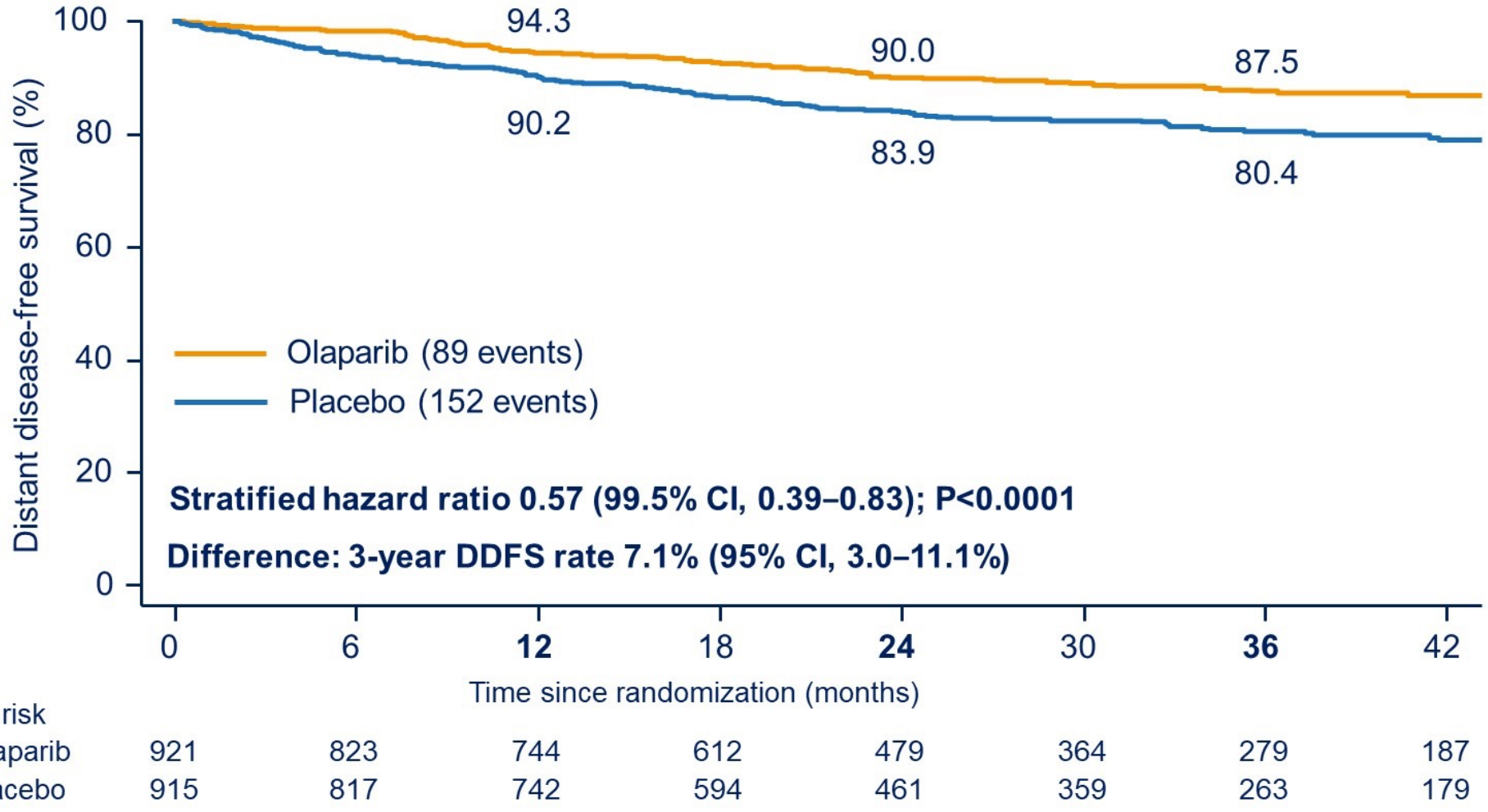
IDFS
P<0.005

DDFS and OS only tested if IDFS significant

DDFS
P<0.005

OS
P<0.01

Recycling of alpha for conservation future analyses



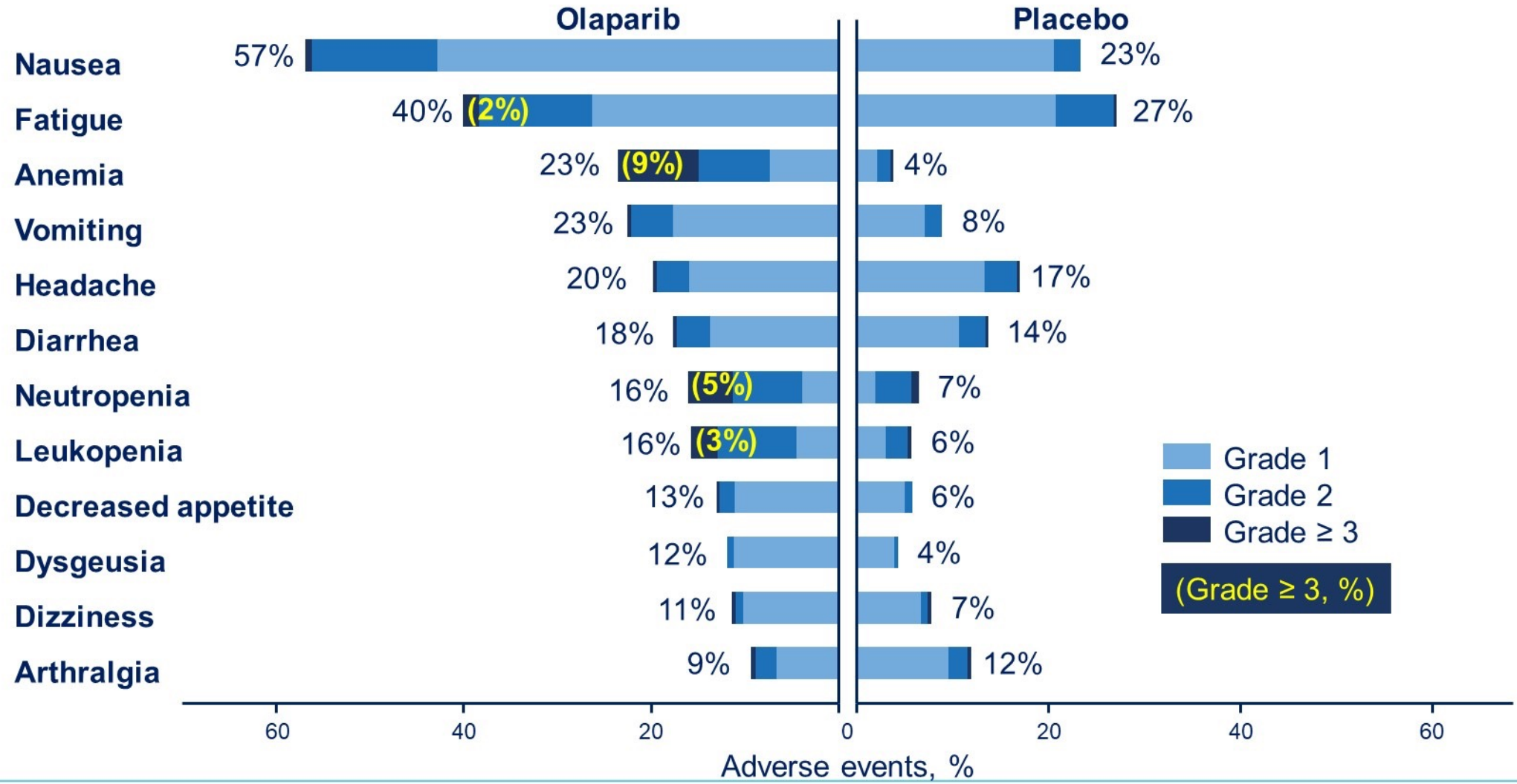
No. at risk

Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

OlympiA: Adverse events of any grade ≥ 10%



Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

Agenda

Module 1: Evolving Clinical Decision-Making for Patients with ER-Positive, HER2-Negative Localized Breast Cancer

- Dr O'Regan: A 54-year-old postmenopausal woman with ER-positive, PR-negative, HER2-negative pT1cN1 breast cancer
- Dr Mahtani: A 43-year-old woman with 6-cm ER-positive, HER2-negative localized breast cancer

Module 2: Selection and Sequence of Therapy for ER-Positive, HER2-Negative Metastatic BC (mBC)

- Dr O'Regan: A 55-year-old woman with ER-positive, PR-negative, HER2-negative mBC
- Dr Mahtani: A 50-year-old woman with ER-positive, HER2-negative mBC – germline BRCA2 mutation
- Dr Partridge: A 37-year-old woman with ER-positive, HER2-negative mBC – germline BRCA1 mutation

Module 3: New Directions in the Treatment of Triple-Negative Breast Cancer (TNBC)

- Dr Partridge: A 52-year-old woman with metastatic TNBC – PD-L1-positive

RTP RESEARCH TO PRACTICE

A patient with ER-positive, HER2-negative breast cancer receives palbociclib/fulvestrant after relapse on adjuvant letrozole. Genomic testing reveals a PIK3CA mutation. What would be your most likely next endocrine therapy?

1. Alpelisib
2. Alpelisib/fulvestrant
3. Alpelisib with other endocrine therapy
4. Other

A patient with ER-positive mBC experiences asymptomatic disease progression on palbociclib/letrozole. Genomic testing reveals a PIK3CA mutation. Her baseline fasting glucose is 130 mg/dL and hemoglobin A1c = 6.5%. Would you recommend alpelisib/fulvestrant for this patient?

1. No
2. Yes, with standard-dose alpelisib
3. Yes, with reduced-dose alpelisib

Case Presentation – Dr O'Regan: A 55-year-old woman with ER-positive, PR-negative, HER2-negative metastatic breast cancer

Dr Ruth O'Regan

- Presents with hip pain
- Systemic imaging: Liver and bone metastases
- Liver biopsy: Adenocarcinoma, ER-positive, PR-negative, HER2-negative
- Palbociclib with anastrozole → PD 18 months later
- Liver biopsy sent for NGS: PI3-kinase mutation
- Alpelisib/fulvestrant x 5 months, with hyperglycemia requiring metformin, dose reductions

Questions

- If this patient had received fulvestrant with the CDK4/6 inhibitor, what endocrine therapy would you have partnered with alpelisib?
- How commonly are you seeing hyperglycemia in patients receiving alpelisib? Rash?
- What would you recommend as her next treatment if her disease progresses? Have you used everolimus in a patient who has already received alpelisib?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Mahtani: A 50-year-old woman with ER-positive, HER2-negative metastatic breast cancer and a germline BRCA2 mutation

Dr Reshma Mahtani

- A post-menopausal woman who initially presented for consideration of neoadjuvant chemotherapy for a cT3N1 ER+/HER2- breast cancer
  - Imaging: Multiple lesions suspicious for bone metastases, mediastinal adenopathy, elevated markers
  - Patient declined a biopsy; no family history of breast, ovarian, or prostate cancer
- Palbociclib/letrozole with good response but eventual progression in the breast and bone
- No PIK3CA mutation identified
- Fulvestrant with no response after 3 months
- Offered BRCA testing (in the absence of family history) and found to have a germline BRCA2 mutation
- 6/2020: Talazoparib with ongoing response

Questions

- How are you sequencing a PARP inhibitor in a patient with ER-positive disease? If you had known that she carried a BRCA mutation, would you have used the PARP inhibitor before fulvestrant?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Partridge: A 37-year-old woman with ER-positive, HER2-negative metastatic breast cancer and a germline BRCA1 mutation

Dr Ann Partridge

- 2012: Initial diagnosis of left-sided IDC, grade 3, ER/PR positive and HER2 +3 (BWH - marked HER2 heterogeneity)
  - s/p bilateral mastectomies and adjuvant AC-TH; tamoxifen with zoledronic acid
- Genetic testing: germline BRCA1 mutation
- 5/2019: Increasing shortness of breath and back pain; CTA revealed a left-sided pleural effusion, a patchy LUL opacity, lytic lesions in the sternum and T10, several rib fractures and a suspected liver metastasis
  - Biopsy of left axillary lymph node: IDC, grade 2, ER positive 95%-strong, PR positive 5%-weak, HER2 +2, FISH negative (ratio = 1.9)
- 6/2019: Starts first line olaparib

Questions

- What would you recommend as first-line therapy for a patient with advanced HR-positive, HER2-negative breast cancer in the setting of a known BRCA1 mutation? Do you go with a PARP inhibitor or an antiestrogen with a CDK4/6 inhibitor? Or all of the above?

RTP RESEARCH TO PRACTICE

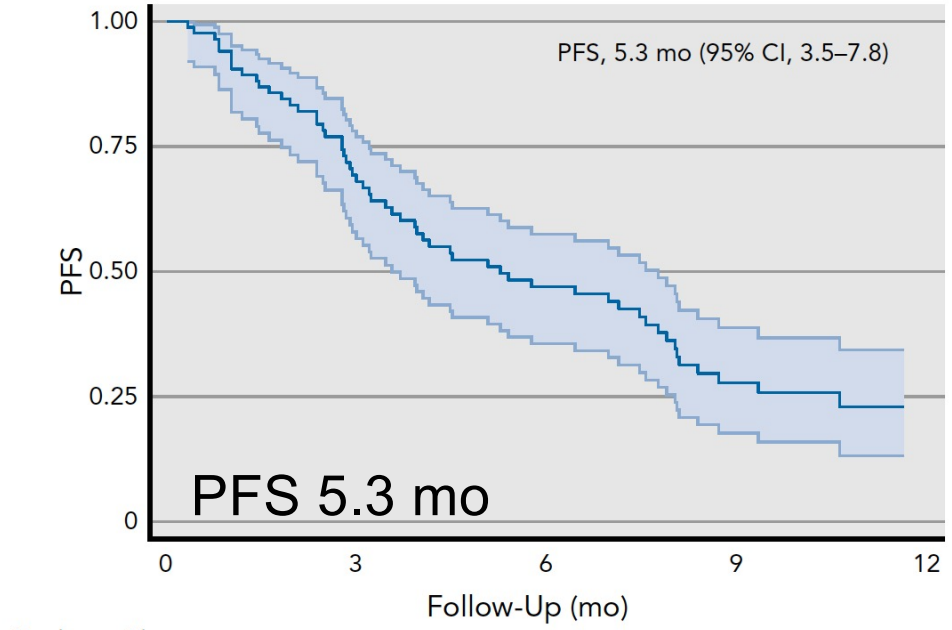
Overall Survival Benefit with CDK4/6 Inhibitors for ER-Positive, HER2-Negative Metastatic Breast Cancer

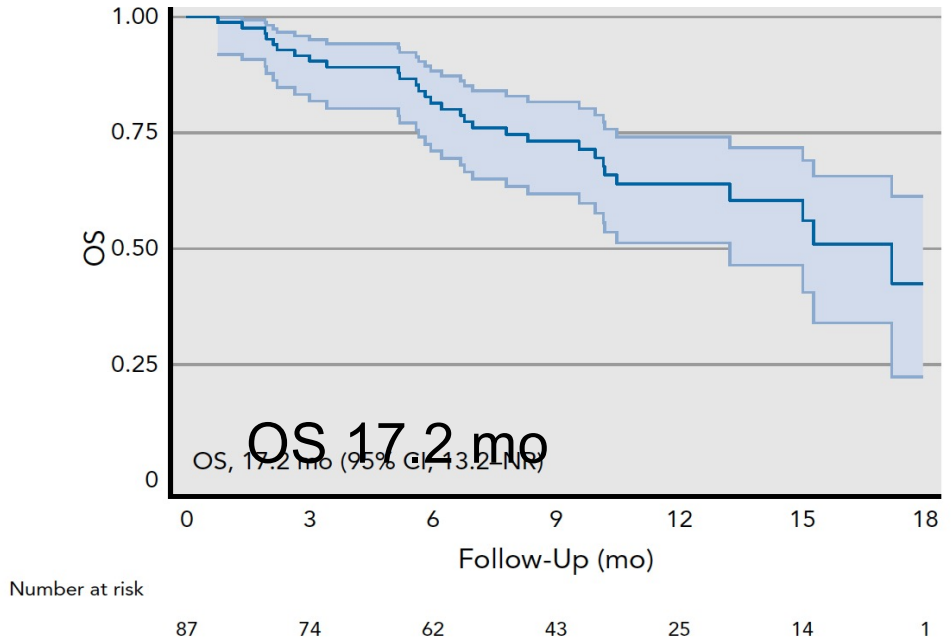
- **MONALEESA-7[1]: Ribociclib + endocrine therapy**
  - HR (95% CI): 0.763 (0.608-0.956); Months: 58.7 vs 48.0
- **MONALEESA-3[2]: Ribociclib + fulvestrant**
  - HR (95% CI): 0.726 (0.588-0.897); Months: 53.7 vs 41.5
- **MONARCH 2[3]: Abemaciclib + fulvestrant**
  - HR (95% CI): 0.757 (0.606-0.945); Months: 46.7 vs 37.3
- **PALOMA-3[4]: Palbociclib + fulvestrant**
  - HR (95% CI): 0.81 (0.65-0.99); Months: 34.8 vs 28.0

[1] Tripathy D et al. SABCS 2020; [2] Slamon D et al. ASCO 2021; [3] Sledge G et al. *JAMA Oncology* 2020; [4] Rugo H et al. *Oncologist* 2021

CDK4/6i after CDK4/6i

- 6 institution retrospective analysis
  - 87 patients treated with abemaciclib post palbociclib
  - 9.2% stopped abemaciclib due to toxicity without progression
  - 71.3% received non-sequential therapy with ≥1 intervening non-CDK4/6i regimen
  - Endocrine partners
    - Fulvestrant: 47.1%; aromatase inhibitor: 27.6%; monotherapy: 19.5%
- Efficacy
  - 36.8% received abemaciclib for ≥ 6 months
  - There was no relationship between the duration of clinical benefit on palbociclib and the subsequent duration of treatment on abemaciclib
- Rapid progression on abemaciclib associated with RB1, ERBB2, and CCNE1 alterations were noted among patients with rapid progression on abemaciclib.

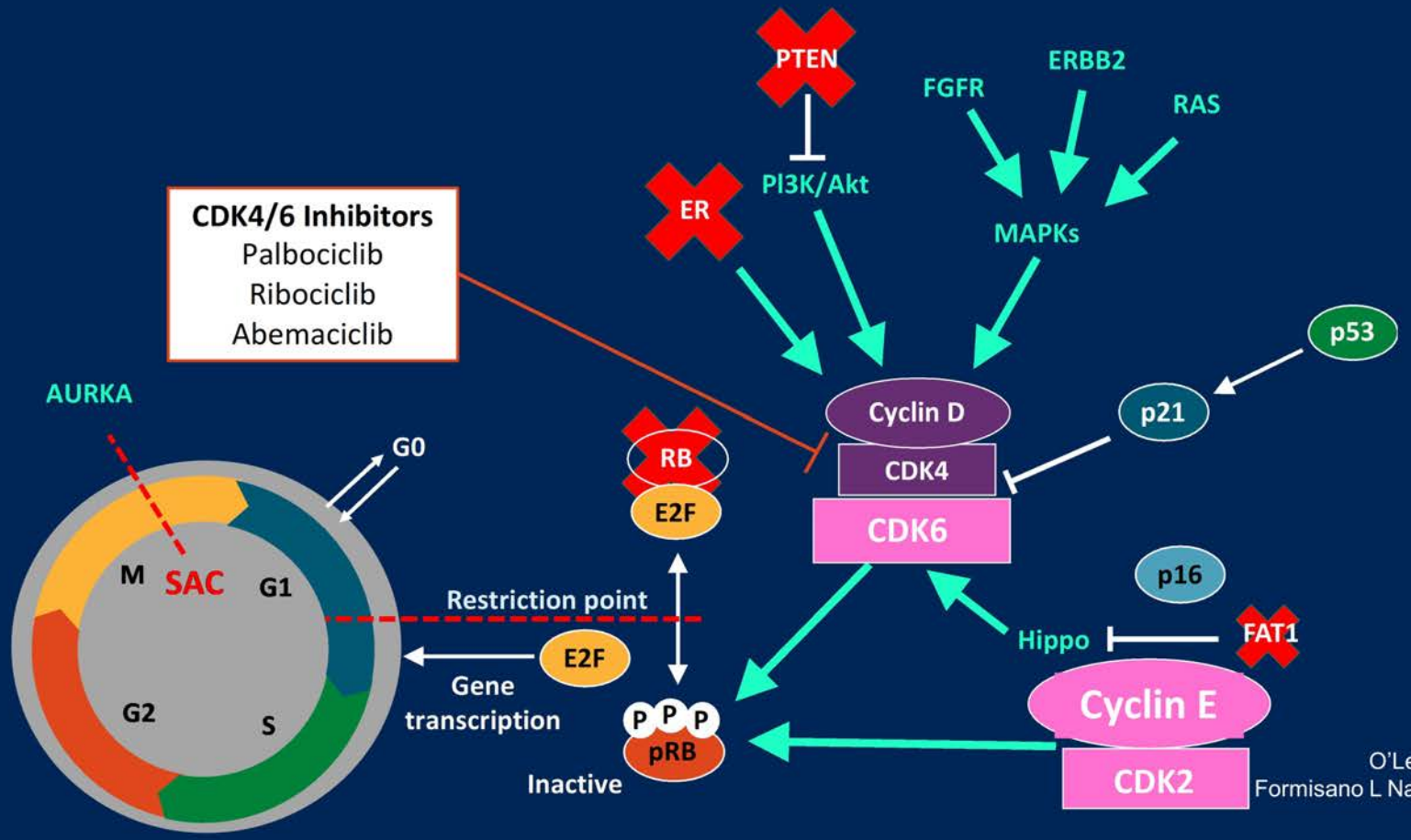




Wander S et al. JNCCN 2021

Courtesy of Hope S Rugo, MD

Mechanisms of Resistance to CDK4/6 inhibitors



O'Leary B Cancer Discov 2018; 8:1390-1403
Formisano L Nature Communications 2019; 10: 1373-64
Razavi P ASCO 2019. Abstract 1009
Costa C Cancer Discov 2020;10:72–85
Wander SA Cancer Discov 2020;10:1174–93

Bedard, Poster Discussion ASCO 2021

Courtesy of Hope S Rugo, MD

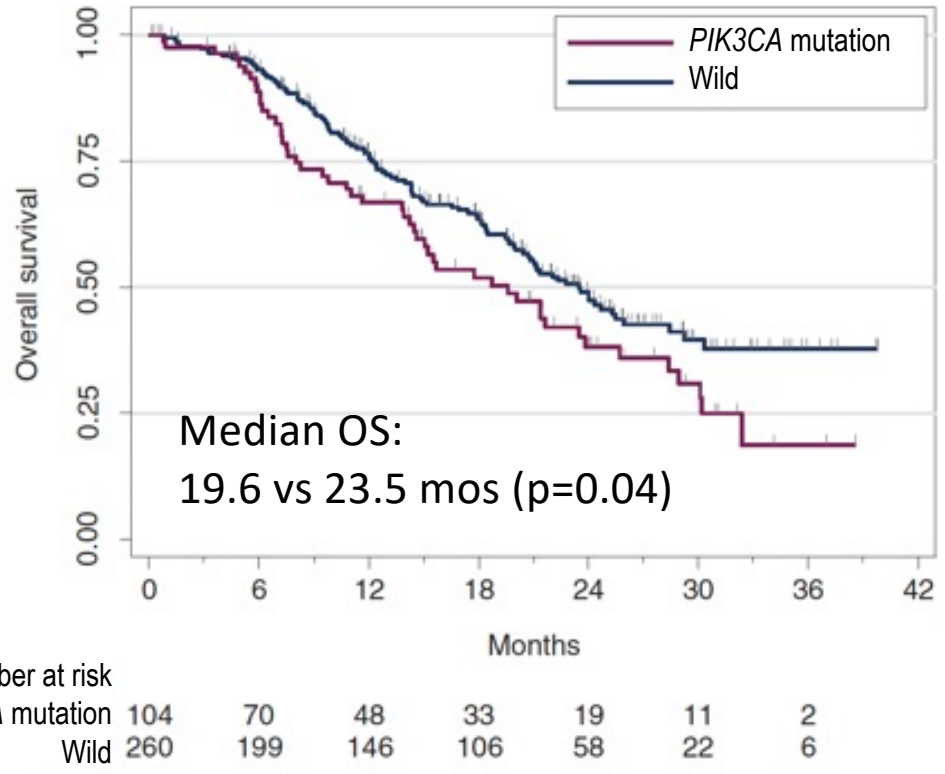
Gain-of-Function PI3K Mutations

- PI3K pathway hyperactivation due to *PIK3CA* mutations contributes to endocrine resistance
- *PIK3CA* is one of the most frequently mutated genes in BC, occurring in approximately 40% of HR+, HER2– ABCs
- The presence of a *PIK3CA* mutation is a negative prognostic factor in HR+, HER2– ABC

Impact of PIK3CA Mutations in SAFIR02

PIK3CA Mutations in 28% of HR+/HER2- MBC

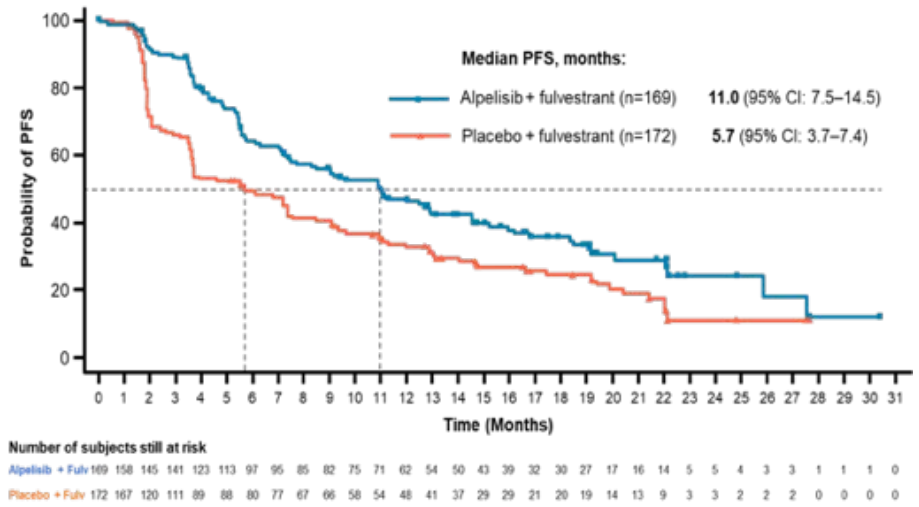
(associated with older age and lower tumor grade)



Mukohara T. *Breast Cancer (Dove Med Press)*. 2015;7:111-123; Cancer Genome Atlas Network. *Nature.* 2012;490(7418):61-70; Mollon L, et al. AACR 2018. Poster 1207; Moynahan ME, et al. *Br J Cancer.* 2017;116(6):726-730; Tolaney S, et al. AACR 2019. Abstract 4458; Di Leo A, et al. *Lancet Oncol*. 2018;19(1):87-100; 7. Sobhani N, et al. *J Cell Biochem*. 2018;119(6):4287-4292; Mosele F, et al. *Ann Oncol*. 2020;31(3):377-386; Lai YL, et al. *Ann Surg Oncol*. 2008;15(4):1064-1069.

Courtesy of Hope S Rugo, MD

SOLAR-1: Primary Endpoint of Locally Assessed PFS in the *PIK3CA*-mutant Cohort with Alpelisib, an Alpha Specific PI3K Inhibitor



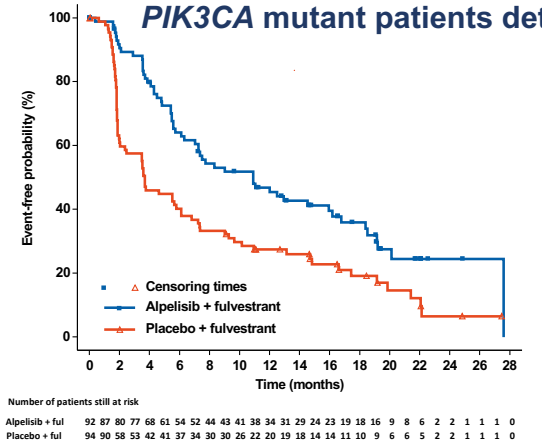
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
At final PFS analysis, superiority was declared if one-sided, stratified log-rank test *P* value was ≤ 0.0199 (Haybittle–Peto boundary).
[a] Mutation status determined from tissue biopsy.

Data cut-off: Jun 12, 2018	ALP + FUL (n = 169)	PBO + FUL (n = 172)
Number of PFS events, n (%)	103 (60.9)	129 (75.0)
Progression	99 (58.6)	120 (69.8)
Death	4 (2.4)	9 (5.2)
Censored	66 (39.1)	43 (25.0)
Median PFS (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85)	
One-sided *P* value	0.00065	

Similar results when PI3K mutation determined in plasma using ctDNA

Only 6% had prior exposure to a CDK4/6i

Locally Assessed PFS by Tissue or Plasma ctDNA Mutation Status



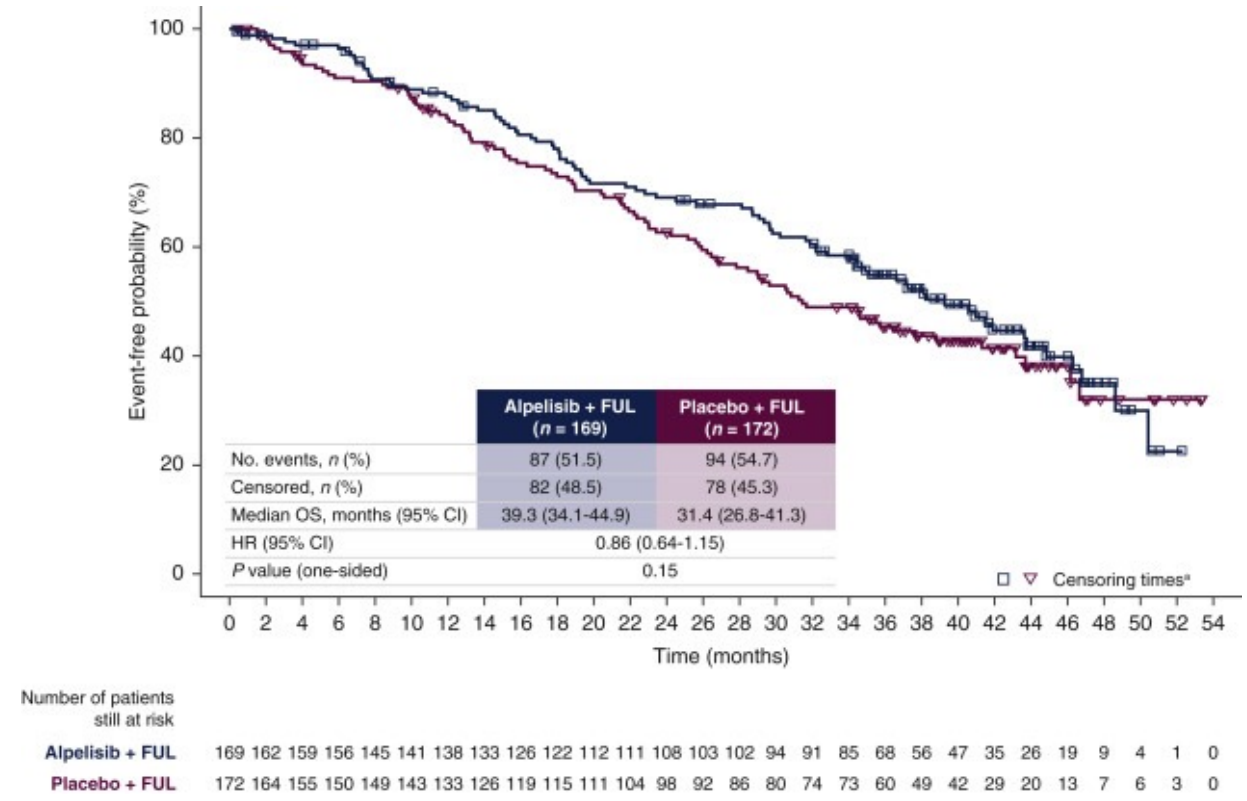
	ALP + FUL		PBO + FUL		
	Event n/N (%)	Median PFS	Event n/N (%)	Median PFS	HR
Patients with *PIK3CA* mutation: tissue	103/169 (60.9)	11.0	129/172 (75.0)	5.7	0.65
Patients with *PIK3CA* mutation: plasma	57/92 (62.0)	10.9	75/94 (79.8)	3.7	0.55
Patients without *PIK3CA* mutation: tissue	49/115 (42.6)	7.4	57/116 (49.1)	5.6	0.85
Patients without *PIK3CA* mutation: plasma	92/181 (50.8)	8.8	103/182 (56.6)	7.3	0.80

ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival; QD, once daily.

Courtesy of Hope S Rugo, MD

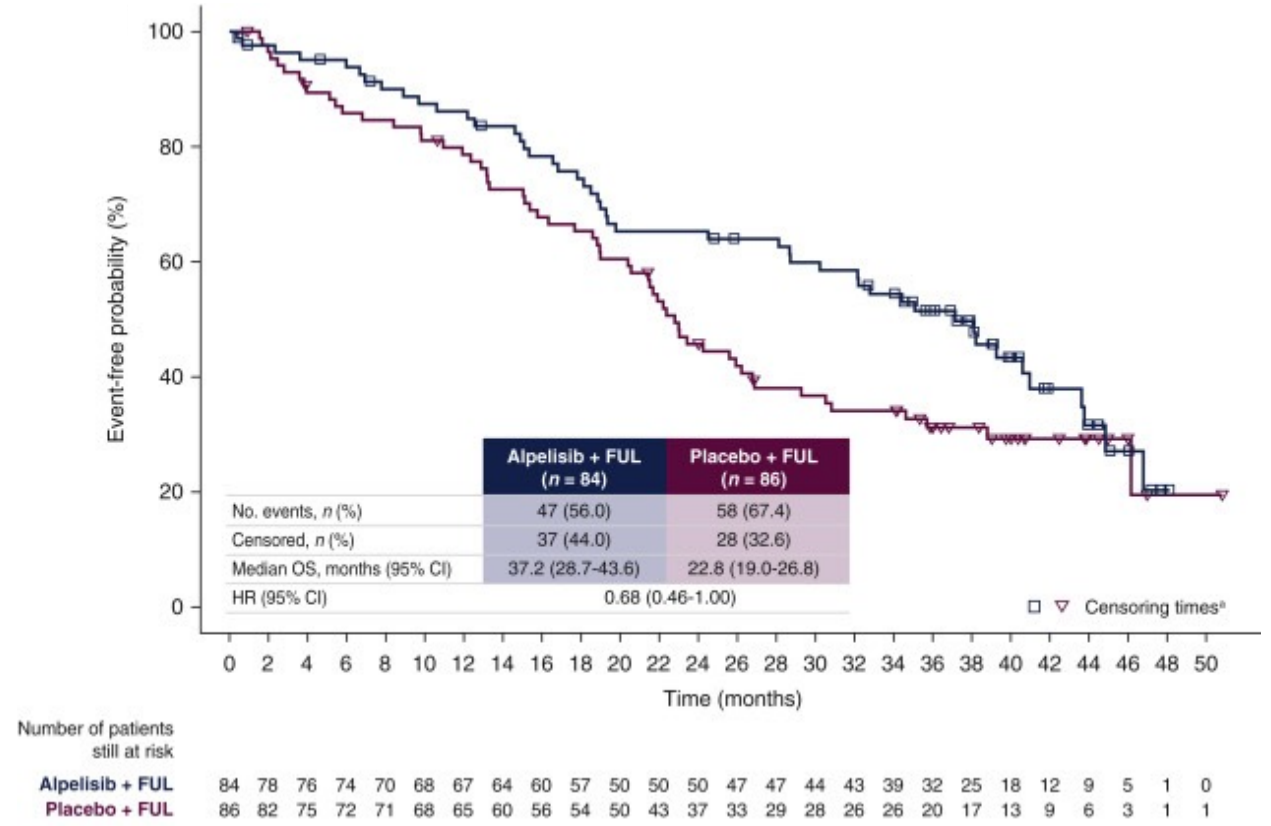
Andre et al, NEJM 2019;
Juric et al, SABCS 2018

SOLAR-1: Overall Survival



- mOS prolonged by 7.9 mo for pts receiving alpelisib + fulvestrant
- Final OS in the PIK3CA mutant cohort did not cross the pre-specified efficacy boundary (1-sided p≤0.0161)

Andre et al, Ann Oncol 2021



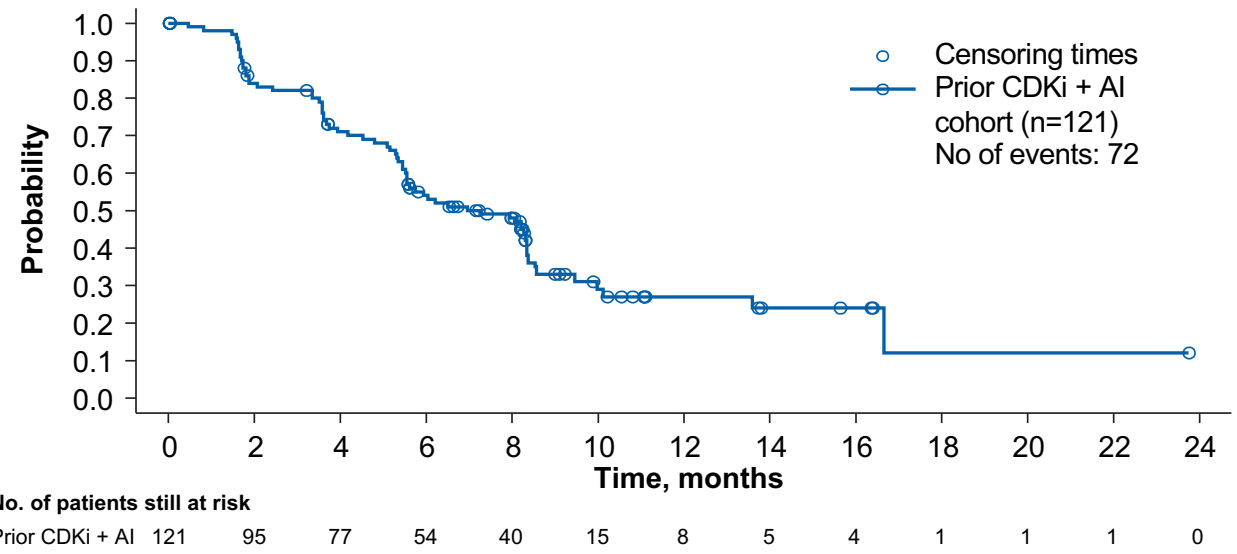
- Overall survival in patients with *PIK3CA*-mutated cancer with lung/liver metastases

Courtesy of Hope S Rugo, MD

BYLieve Cohort A: Primary Endpoint and PFS Results

(prior AI + CDK4/6i as last treatment)

Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)



The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

- Median OS 17.3 months
- In SOLAR-1, 44.4% of patients in the *PIK3CA*-mutant cohort with prior CDKi treated with alpelisib plus fulvestrant were alive without disease progression at 6 months

- Median PFS Cohort B: 5.7 months; letrozole/alpelisib with 82% prior PD on AI; 46% alive and without PD at 6 months

Courtesy of Hope S Rugo, MD

Rugo et al, Lancet Oncol 2021; Rugo et al, SABCS 2020

PFS Effect of Alpelisib Over Standard Treatments in Real-World Setting

Analysis Method (In Patients With *PIK3CA* Mutation)	**BYLieve Prior CDKi +AI (Cohort A) Alpelisib + Fulvestrant median-PFS (mo)** (95% CI), n	**Flatiron/FMI Standard Treatment median-rwPFS (mo)** (95% CI), n
Unadjusted results	**7.3** (5.6-8.3), n=120	**3.6** (3.1-6.1), n=95
Weighting by odds	**7.3** (5.6-8.3), n=120	**3.7** (3.1-6.1), n=116
Propensity score matching	**8.0** (5.6-8.6), n=76	**3.5** (3.0-5.4), n=76
Exact matching	**6.5** (5.3-8.3), n=61	**3.4** (2.9-3.9), n=61

Matched analysis comparing BYLieve with RWE standard treatment in post-CDK4/6i setting further supports use of alpelisib + fulvestrant

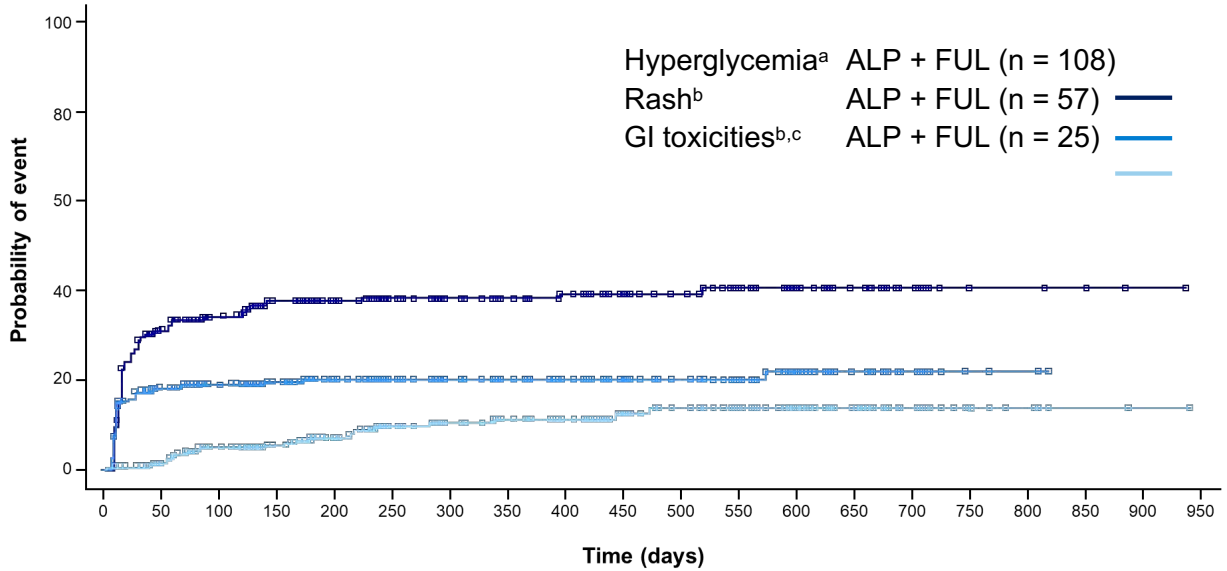
PFS comparison is based on PFS per RECIST v1.1 in BYLieve and real-world PFS in Flatiron/FMI.

Courtesy of Hope S Rugo, MD

Time Course of Adverse Events in SOLAR-1

- The most common grade ≥3 AEs in the ALP arm were hyperglycemia, rash, and diarrhea
- In the ALP arm, hyperglycemia and/or rash were typically experienced in the first few weeks of treatment with ALP + FUL, whereas GI toxicities could occur at any time during study therapy
- Median time to onset and median time to improvement by ≥1 grade are shown in the table below

Probability of First Occurrence of Grade 3 AESI Events



Time to Onset and Time to Improvement of AESIs

	Median time to onset, days	Median time to improvement by ≥1 grade, days
Hyperglycemia	15	6
Rash	13	11
Diarrhea	139	18

AE, adverse event; AESI, adverse event of special interest; ALP, alpelisib; FUL, fulvestrant; GI, gastrointestinal; PBO, placebo.

[a] Based on laboratory values rather than single preferred term.
[b] Based on grouped terms.
[c] Of the grade ≥ 3 gastrointestinal (GI) toxicities, 76% of them were grade ≥ 3 diarrhea.

Rugo HS et al, Annals Onc 2020

Courtesy of Hope S Rugo, MD

FAKTION: Capivasertib + Fulvestrant for AI-Resistant ER-Positive, HER2-Negative mBC

- Phase II study of capivasertib + fulvestrant vs placebo + fulvestrant (N = 140)
  - Relapse or progression on an AI
  - Capivasertib (AZD5363): selective, oral AKT inhibitor
- Capivasertib + fulvestrant improved PFS in endocrine-resistant mBC vs placebo + fulvestrant
  - Primary endpoint met
  - Trend toward improvement in OS
- Ongoing Phase III CAPitello291 Trial
- IPATunit150: ipatasertib +/- palbociclib and fulvestrant

Outcome	CAP + FULV (n = 69)	PBO + FULV (n = 71)
Median PFS, mos	10.3	4.8
	HR: 0.57 *P* = .0035	
Median OS, mos	26.0	20.0
	HR: 0.59 *P* = .071	

- Similar benefit was observed in patients with PI3K/AKT/PTEN-activated and nonactivated tumors
- 39% of patients in the capivasertib + fulvestrant arm required dose reductions, primarily due to diarrhea and rash, and 12% discontinued due to toxicity

Jones RH, et al. Lancet Oncol 2020.

Courtesy of Hope S Rugo, MD

Agenda

Module 1: Evolving Clinical Decision-Making for Patients with ER-Positive, HER2-Negative Localized Breast Cancer

- Dr O'Regan: A 54-year-old postmenopausal woman with ER-positive, PR-negative, HER2-negative pT1cN1 breast cancer
- Dr Mahtani: A 43-year-old woman with 6-cm ER-positive, HER2-negative localized breast cancer

Module 2: Selection and Sequence of Therapy for ER-Positive, HER2-Negative Metastatic BC (mBC)

- Dr O'Regan: A 55-year-old woman with ER-positive, PR-negative, HER2-negative mBC
- Dr Mahtani: A 50-year-old woman with ER-positive, HER2-negative mBC – germline BRCA2 mutation
- Dr Partridge: A 37-year-old woman with ER-positive, HER2-negative mBC – germline BRCA1 mutation

Module 3: New Directions in the Treatment of Triple-Negative Breast Cancer (TNBC)

- Dr Partridge: A 52-year-old woman with metastatic TNBC – PD-L1-positive

RTP RESEARCH TO PRACTICE

A 35-year-old woman with triple-negative breast cancer receives neoadjuvant anthracycline/taxane therapy followed by surgery and capecitabine but 1 year later develops PD-L1-negative, BRCA-negative metastatic disease. What would be your next treatment?

1. Chemotherapy
2. Chemotherapy + anti-PD-1/PD-L1 antibody
3. Sacituzumab govitecan
4. Other

Case Presentation – Dr Partridge: A 52-year-old woman with metastatic TNBC – PD-L1-positive

Dr Ann Partridge

- 10/2018: Initially diagnosed with left-sided TNBC
  - Neoadjuvant dd-ACT with an excellent, but not full response
  - Left mastectomy and SLNB → adjuvant capecitabine x 6 cycles
- Presented with left chest wall pain and was found to have recurrent disease in three areas in the left chest wall, including 2 chest wall nodules and one bone/rib lesion
- PD-L1-positive TNBC
- Atezolizumab/*nab*-paclitaxel, painful chest wall lesion resolved after first cycle

Questions

- Which assay are you using to assess PD-L1 levels and why?
- How do you sequence therapy in a patient with metastatic TNBC given new agents such as atezolizumab/*nab*-paclitaxel and sacituzumab govitecan? Which ones should we be reaching for first and why?

RTP RESEARCH TO PRACTICE

pCR rates in randomized TNBC neoadjuvant studies

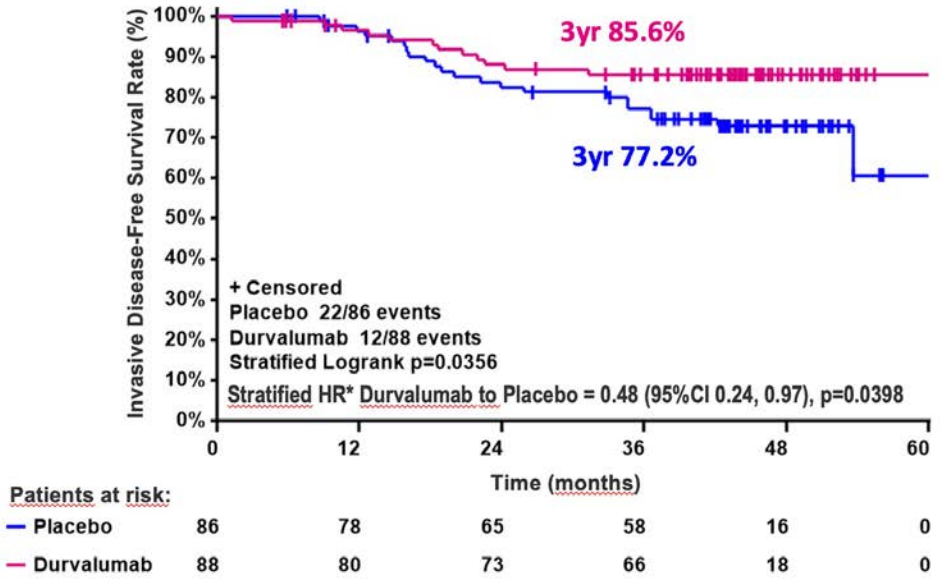
GeparNUEVO	NeoTRIPaPD-L1	KEYNOTE-522	IMpassion 031
Nab-paclitaxel -> EC q2 week +/- Durvalumab (no adj)	Nab-paclitaxel + Carbo weekly 2 on / 1 off x 8 +/- Atezolizumab (no adj)	Paclitaxel + Carbo -> AC/EC q3 week +/- Pembrolizumab 1 year	Nab-paclitaxel -> AC q2 week +/- Atezolizumab 1 year
pCR = 53.4% vs 44.2% Δ 9.2% (n=174)	pCR = 43.5% vs 40.8% Δ 2.7% (n=280)	pCR = 64.8% vs 51.2% Δ 13.6% (n=602) pCR = 63% vs 55.6% Δ 7.5% (n=1174)	pCR = 57.6% vs 41.1% Δ 16.5% (n=333)

Courtesy of Melinda Telli, MD

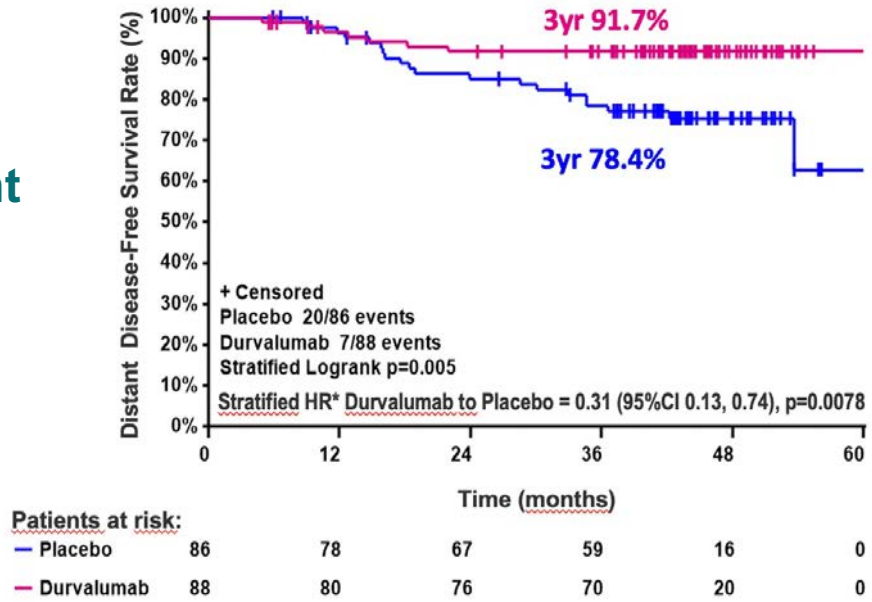
GeparNUEVO Secondary Endpoints

Median follow-up > 3.5 years

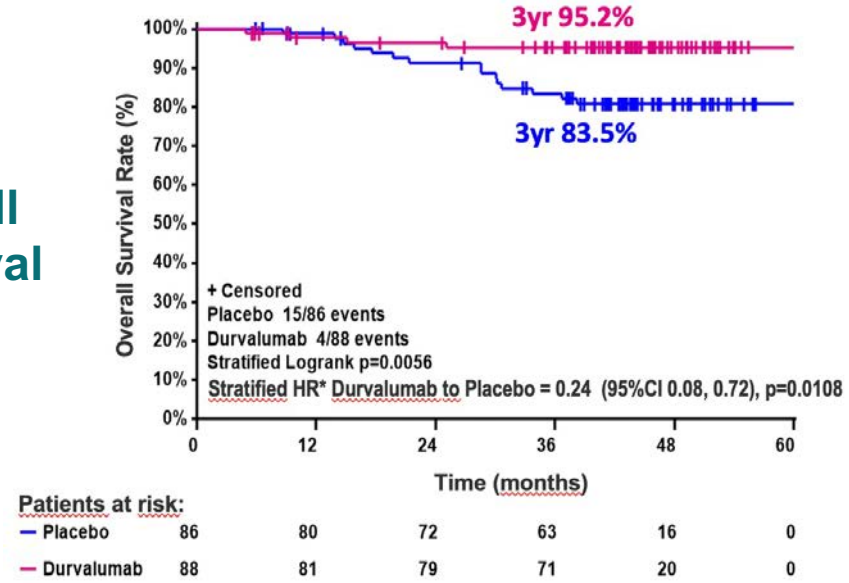
Invasive DFS



Distant DFS

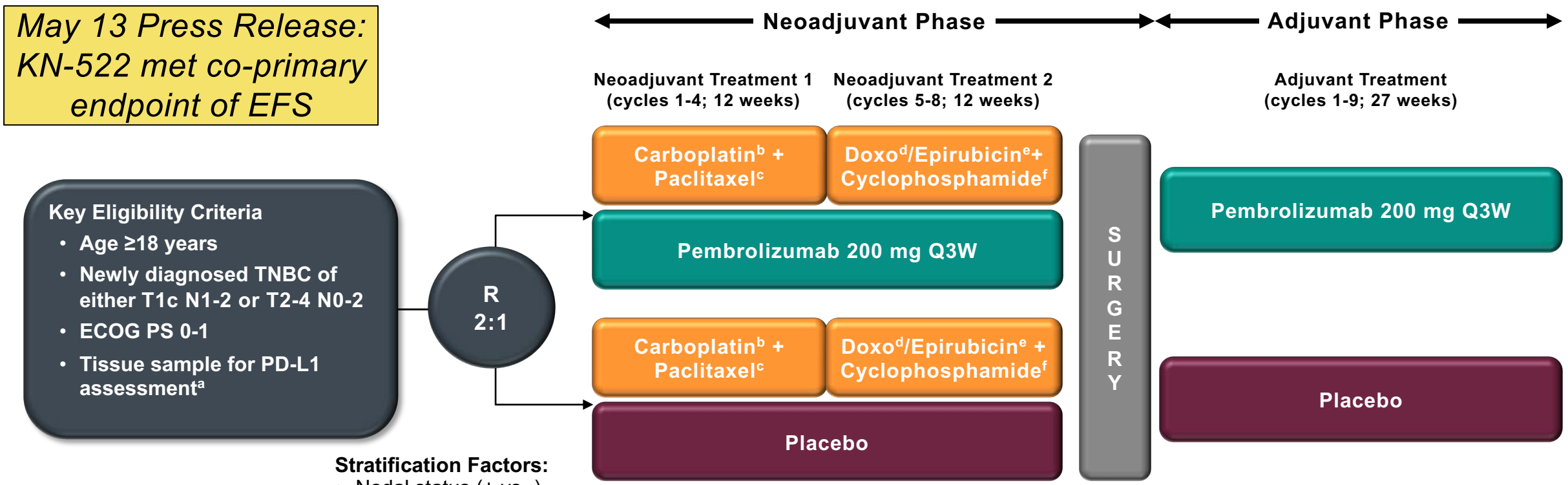


Overall Survival



KEYNOTE-522 Study Design (NCT03036488)

May 13 Press Release: KN-522 met co-primary endpoint of EFS

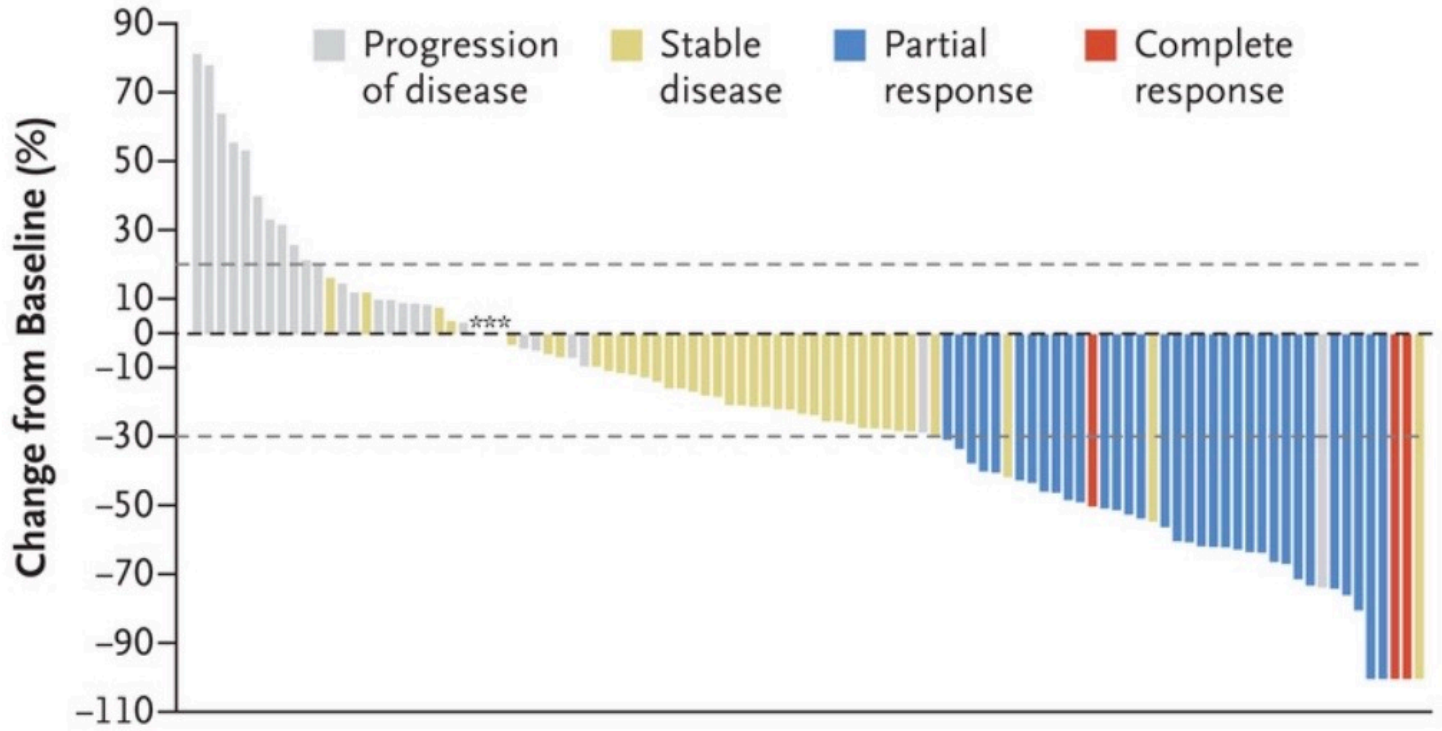


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

Courtesy of Melinda Telli, MD

Phase I/II Sacituzumab Govitecan (IMMU132) in Metastatic TNBC



Bardia A, et al. NEJM 2019

Median prior number of therapies = 3 (range 2-10)

Dose = 10 mg/kg IV days 1, 8 every 21 days

Response rate = 33%

Duration of response = 7.7 months

<u>Common side effects:</u>
Neutropenia, Anemia, Diarrhea, Nausea, Fatigue

ACCELERATED FDA APPROVAL APRIL 22, 2020

Indicated for patients with mTNBC who received at least 2 prior regimens for advanced disease

Courtesy of Melinda Telli, MD

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC

Metastatic TNBC

(per ASCO/CAP)

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be progression occurred within a 12-month period after completion of (neo)adjuvant therapy]

N=529

NCT02574455

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

Endpoints

Primary
- PFS†

Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Exploratory
- **Biomarkers**

Data cutoff: March 11, 2020

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

*TPC: eribulin, vinorelbine, gemcitabine, or capecitabine. †PFS measured by an independent, centralized, and blinded group of radiology experts who assessed tumor response using RECIST 1.1 criteria in patients without brain metastasis. ‡The full population includes all randomized patients (with and without brain metastases). Baseline brain MRI only required for patients with known brain metastasis.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DOR, duration of response; DSMC, Data Safety Monitoring Committee; IV, intravenous; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.
National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02574455.

Courtesy of Melinda Telli, MD

Antibody-Drug Conjugates Under Investigation in Metastatic TNBC

	Trastuzumab deruxtecan	Ladiratuzumab vedotin	Datopotamab deruxtecan
Other name:	DS-8201a	SGN-LIV1A	DS-1062a
Target:	HER2 (IHC 1+ / 2+)	LIV-1	Trop-2
Cytotoxic:	Topoisomerase I inhibitor	MMAE	Topoisomerase I inhibitor

Courtesy of Melinda Telli, MD

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ASCO Highlights and More: Investigators Review Recent Data Sets and Provide Perspectives on Current Oncology Care

A Daylong Multitumor Educational Webinar in Partnership with the Texas Society of Clinical Oncology (TxSCO)

Saturday, June 26, 2021
8:00 AM – 3:00 PM Central Time
(9:00 AM – 4:00 PM Eastern Time)

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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